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Stereogenic quaternary carbon centres
via
Lewis acid catalysed allylborations

by

Jason W. J. Kennedy ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial
fulfillment of the

requirements for the degree of Doctor of Philosophy

Department of Chemistry

Edmonton, Alberta
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University of Alberta

Faculty of Graduate Studies and Research

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Professor Derrick L. J.Clive

Professor Donald S. Matteson

Supervisor writes the date that the thesis is approved by committee here June 26, 2003

Abstract

The generation of stereodefined, quaternary carbon centres remains a major challenge in modern synthetic chemistry. Part I of this thesis describes the preparation of homoallylic alcohol derivatives containing α-quaternary centres with complete diastereocontrol by the stereospecific reaction of geometrically pure, tetrasubstituted allylboronates with aldehydes. The boronates required for these reactions are available with excellent control of the olefin geometry by the *cis*-carbocupration of simple alkynoate esters followed by alkylation with an iodomethaneboronate. The use of an additive in the alkylation step was essential in order to obtain satisfactory yields and stereoselectivities for this process. Chapter 2 of this thesis details the preparation of these substituted allylboronates.

Chapter 3 describes the stereospecific reaction of these γ-disubstituted allylboronates with aldehydes to generate products possessing a stereogenic quaternary carbon centre. The initially formed homoallylic alcohol products of these reactions generally cyclize spontaneously yielding α-methylene-γ-lactones, a known class of cytotoxic compounds and important synthetic intermediates. Enantioselective variants of this reaction, both a novel route using a chiral auxiliary on the 2-carboxyester as well as a dual-auxiliary approach are presented, showing that these additions can be performed with excellent control of the relative and absolute stereochemistry of the products. Further transformation of these α-methylene-γ-lactones is also presented.

Our development of the Lewis acid catalysed allylboration reaction is the single most important result to come from this thesis. Chapter 4 outlines the discovery of this process, from the initial catalyst screenings to the final optimized procedures that allow for the effective catalysed allylboration of aliphatic and aromatic aldehydes. Preliminary forays into enantioselective catalysis and insights into the mechanistic origin of the catalytic effect will also be presented.

Part II of this thesis concerns the development of a novel boron containing chiral auxiliary that is capable of activating an acrylamide dienophile by internal coordination of the carbonyl to an intramolecular boronic ester. Chapter 5 explores the feasibility of this idea and presents the results of a study on rate acceleration and stereoinduction in cycloadditions with this system.

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List of Abbreviations

AB	AB quartet
Ac	Acetyl
Anal.	Elemental Analysis
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Binol	1,1'-Bi-2-Naphthol
Bn	Benzyl
BOC	*tert*-Butoxycarbonyl group
br s	Broad singlet
Bu	*n*-Butyl
(*s*)-Bu	*sec*-Butyl
(*t*)-Bu	*tert*-Butyl
Calcd	Calculated
cat	Catalytic amount
cod	Cyclooctadiene
Cy	Cyclohexyl group
dba	Dibenzylideneacetone
DCC	1,3-Dicyclohexylcarbodiimide
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
de	Diastereomeric excess
DIBAL	Diisobutylaluminum hydride
DICHED	1,2-Dicyclohexylethanediol
DMAP	4-(*N*, *N*-Dimethylamino)pyridine
DMEU	1,3-Dimethyl-2-imidazolidinone
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron Impact
equiv.	Equivalents
er	Enantiomeric ratio

ES	Electrospray
Et	Ethyl
(*c*)-Hex	Cyclohexyl
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared spectroscopy
LA	Generic Lewis acid
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
ML_n	Generic metal with ligands
mp	Melting point
nOe	Nuclear Overhauser Effect
Nu	Generic nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Trifluoromethanesulfonate
Ph	Phenyl
PMA	Phosphomolybdic acid
Pr	*n*-Propyl
(*i*)-Pr	Isopropyl
pTSA	*para*-Toluenesulfonic acid
PyBOX	2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine
q	Quartet
qt	Quartet of triplets
R	Generic alkyl group
RT	Room temperature
s	Singlet
SAMP	(*S*)-1-Amino-2-methoxymethylpyrrolidine
t	Triplet
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TMEDA	*N*, *N*, *N'*, *N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPS	*tert*-Butyldiphenylsilyl
Ts	*para*-Toluenesulfonyl

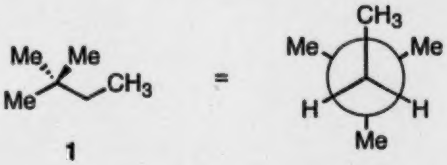
PART I

Chapter 1

Introduction: Construction of Quaternary Carbon Centres

1.1 Introduction

Despite the major advances made in synthetic organic chemistry over the past several decades, the construction of quaternary carbon centres (*i.e.*, carbons bearing four carbon substituents) remains a significant challenge.[1] Part of this challenge derives from the congested nature of these carbon centres which makes unfavourable steric interactions unavoidable. For example, even in simple systems (*e.g.*, 2-dimethylbutane **1**, Figure 1-1), there are no conformations that are free from unfavourable gauche interactions between the terminal methyl group and the methyl groups on the adjacent quaternary centre. Because these steric interactions are unavoidable, any reaction that attempts to prepare a quaternary carbon centre must be energetically more demanding than analogous processes for less substituted centres.



1

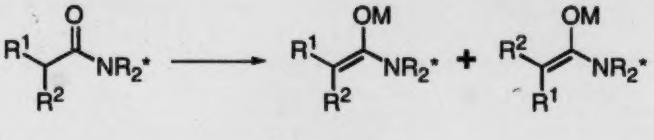
Figure 1-1. 2,2-Dimethylbutane **1** with Newman projection.

Besides presenting an intellectual challenge for modern synthetic chemists, these sterically demanding centres are present in many interesting natural products. Since quaternary carbon centres in natural products often bear four, non-equivalent substituents, the challenges of stereoselective synthesis must also be factored into the preparation of these centres. Specific strategies are usually found for the installation of a particular centre in a given target molecule, however, very few general strategies exist for the preparation of quaternary carbon centres. This thesis deals with the construction of stereogenic quaternary carbon centres via allylboration chemistry. Though other approaches to quaternary carbon centres have been published (*e.g.*, Michael additions,[2] ring-closing metathesis,[3] rearrangements[4]), in the interest of conciseness, the remainder of this introduction will focus only on routes that are based on alkylation and allylation chemistry.

1.2 Quaternary Carbon Centres Through Enolate Alkylation Chemistry

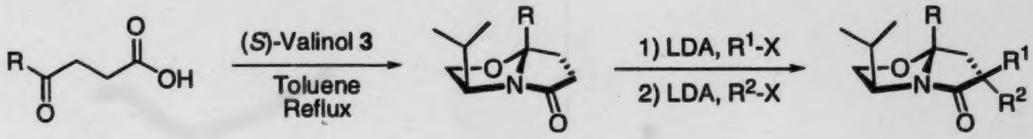
1.2.1 Alkylation of chiral bicyclic lactams

Conceptually, one of the simplest ways to make a quaternary carbon centre is via the alkylation of an α-disubstituted enolate. The major drawback to this strategy is that the configuration of the enolate can exist in two forms, the *E*- or *Z*-configuration (Scheme 1-1). Thus, even if a given alkylation system shows good facial control (*i.e.*, the incoming nucleophile is directed exclusively to the top or bottom face of the enolate), the geometry of the enolate must be controlled in order to achieve high selectivity in these reactions.



Scheme 1-1

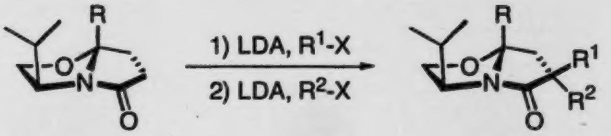
An effective approach to this problem is to confine the enolate within a small ring. This idea was elaborated in the chiral non-racemic bicyclic lactam chemistry of Meyers and co-workers (Scheme 1-2).[5] In the example shown below, ketoacid **2a** is condensed with a chiral amino alcohol **3** (here (*S*)-valinol) to give bicyclic lactam **4**. Sequential dialkylation of this intermediate yields product **5** which now bears a quaternary carbon centre. In these alkylations, the electrophile always approaches from the *endo* face of the substrate. Thus, the selectivity of the first alkylation, though usually quite good, is irrelevant since the resulting stereogenic centre is planarized during subsequent alkylation. One beneficial effect of this predictable path of approach of the electrophile is that the stereochemistry of the final quaternary centre is not determined by the nature of the R groups, but rather by the order in which the electrophiles are introduced.



2a **4** **5**

Scheme 1-2

As can be seen from Table 1-1, the yields and selectivities observed for the doubly alkylated products **5** are good to excellent. The differentiation between a methyl and an ethyl group (entries 1 and 2), although low, is noteworthy. After standard purification, products with diastereomeric excesses of over 98% can be routinely obtained.

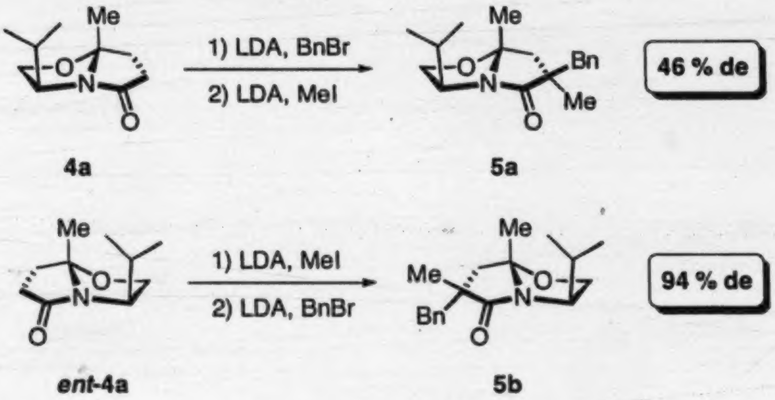


4 **5**

Entry	R	R^1-X	R^2-X	de (%)	Yield (%)
1	Ph	MeI	EtI	76	80
2	Ph	EtI	MeI	82	75
3	Me	Allyl-Br	$PhCH_2Br$	93	77
4	Me	$PhCH_2Br$	Allyl-Br	90	63
5	Me	MeI	$PhCH_2Br$	94	74
6	Me	$PhCH_2Br$	MeI	46	60

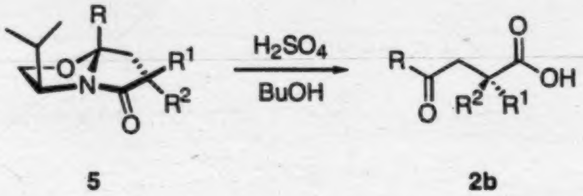
Table 1-1. Yields and selectivities for the double alkylation of bicyclic lactam **4**.

In theory, both enantiomers of a given quaternary centre can be prepared via this route simply by reversing the order in which electrophiles are introduced. However, the selectivity of the second alkylation can vary dramatically with the nature of the electrophile. Generally, alkylation sequences where the second alkylation is with the less reactive electrophile were found to be less selective than sequences where the final alkylation is with the more reactive electrophile (Table 1-1, especially entries 5 and 6). However, since both enantiomers of the amino alcohol used to prepare bicyclic lactam **4** are readily available, either enantiomer of a desired quaternary carbon centre can be prepared by the more selective alkylation sequence. For example, the quaternary carbon centres in **5a** and **5b** in Scheme 1-3 both have the (*R*)-configuration.



Scheme 1-3

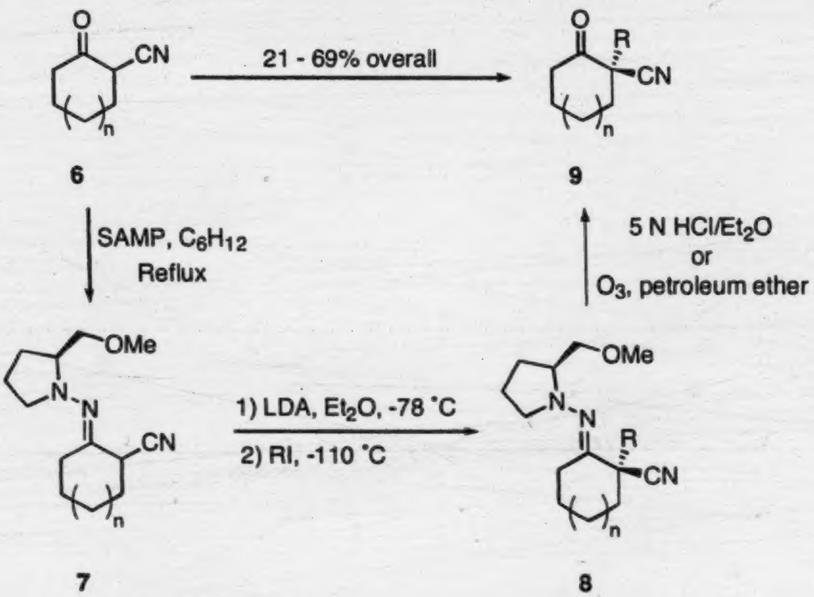
After alkylation, Meyers has shown that the lactams **5** can be hydrolysed to yield disubstituted ketoacids **2b** (Scheme 1-4), or further converted to a wide variety of useful structures, including cyclopentenones, cyclohexenones, indanones and naphthalenones.[5]



Scheme 1-4

1.2.2 Alkylation of SAMP-Hydrazones

Another seminal route to stereogenic quaternary carbon centres comes from the Enders research group. This group found that hydrazone **7**, derived from (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP), can be effectively alkylated with a variety of alkyl iodides. Subsequent hydrolysis of the alkylated hydrazone **8** affords ketone **9** which bears a stereogenic quaternary carbon centre (Table 1-2).[6] Overall yields for the three step process from α-cyanoketone **6** to the alkylated ketone **9** were good and the observed stereoselectivities were excellent. One drawback to this approach is that the substrate scope is not very large, and useful yields and selectivities are only observed with α-cyanocyclohexanones and cyclooctanones. Stereoselectivities are much lower if cycloheptanone, cyclopentanone, or acyclic analogues are used. Similarly, changing the α-cyano group to a carboxyester or phenyl group generally leads to a less selective process.

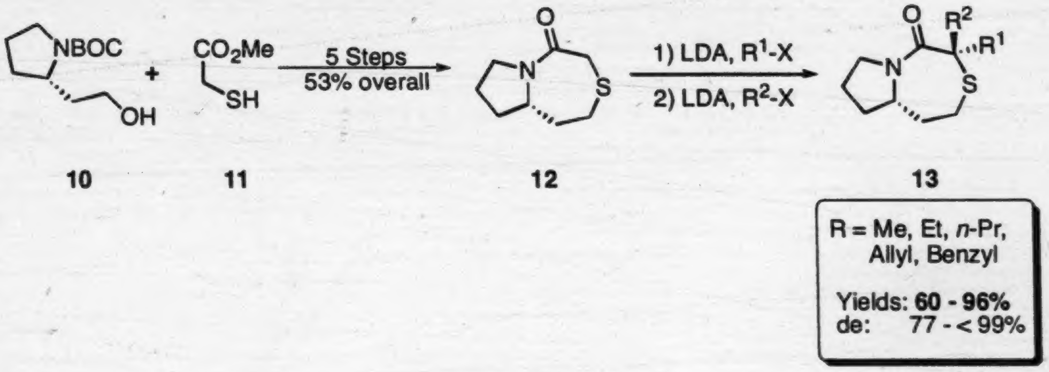


Entry	R	n	Yield of **7** (%)	de of **8**(%)
1	Me	1	68	92
2	Et	1	80	95
3	Pr	1	59	96
4	Et	3	66	94
5	Pr	3	49	94

Table 1-2. Alkylation of 2-cyanocycloalkanone SAMP-hydrazones **7**.

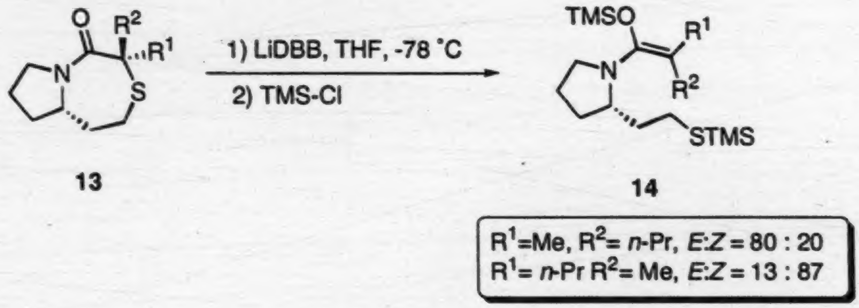
1.2.3 Alkylation of stereodefined acyclic enolates

An alkylation approach which addresses the challenge of stereocontrol with acyclic, tetrasubstituted enolates was recently disclosed by Gleason and co-workers. This group reported a route to quaternary carbon centres via the stereoselective alkylation of acyclic, chiral enolates derived from the radical reduction of chiral, non-racemic, bicyclic lactams **13**.[7a] These lactams are prepared in an efficient multi-step sequence which involves a dialkylation step reminiscent of Meyers' chemistry (Scheme 1-5).[7b]



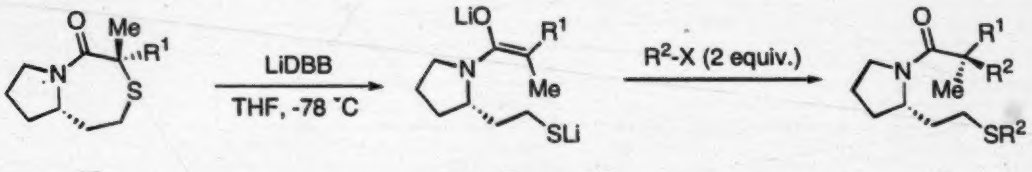
Scheme 1-5

Reductive cleavage of the carbon-sulfur bond in **13** with lithium di-*t*-butylbiphenylide (LiDBB) results in an enolate whose geometry depends on the stereochemistry of the α-carbon and not on the nature of the R groups. Thus, reduction of the (*R*)-isomer of **13** leads to the *E*-enolate, while reduction of the (*S*)-isomer leads to the *Z*-enolate (Scheme 1-6).


1) LiDBB, THF, -78 °C
2) TMS-Cl
TMSO
STMS
13
14
R1=Me, R2= n-Pr, E:Z = 80 : 20
R1= n-Pr R2= Me, E:Z = 13 : 87

Scheme 1-6

The enolates generated in this reduction can be trapped with carbon based electrophiles to give quaternary carbon centres. In an ingenious design aspect of this sequence, the reduction of **13** not only generates the required enolate **15** but also liberates an effective, proline-based chiral auxiliary. Consequently, the subsequent alkylations show high levels of diastereofacial selectivity (Table 1-3).

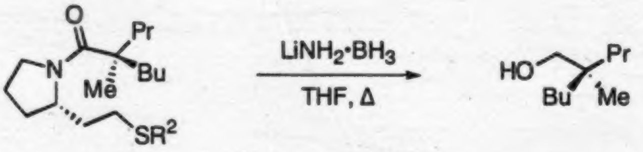


13 **15** **16**

Entry	R^1	R^2-X	Yield of **16** (%)	de (%)
1	Pr	EtI	85	89
2	Et	PrI	83	>95
3	Pr	BuI	71	95
4	Bu	PrI	88	>95

Table 1-3. Quaternary carbon centres from the alkylation of chiral bicyclic lactams **13**.

After alkylation, the chiral auxiliary can be easily cleaved by reduction with LiNH$_2$·BH$_3$ to give the corresponding neopentyl alcohol **17** with no noticeable erosion of stereochemical purity (Scheme 1-7).

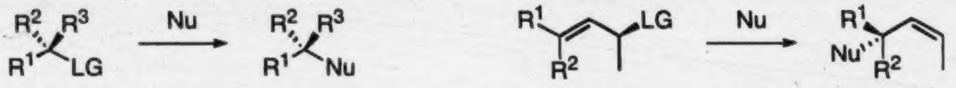


16 **99%** **17, 96% ee**

Scheme 1-7

1.2.4 Quaternary carbon centres from allylic substitution

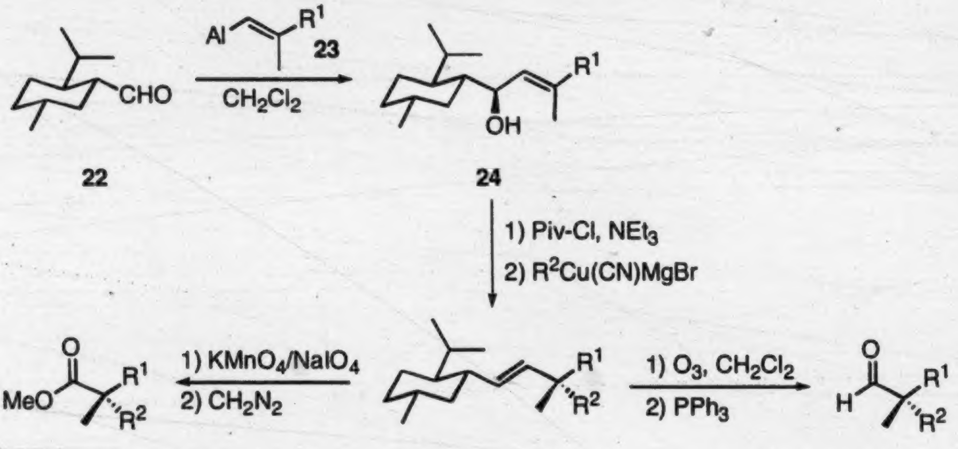
In addition to the enolate chemistry described above, quaternary carbon centres can also be formed from the substitution reaction of a carbon-based nucleophile (Nu) and a tertiary carbon centre bearing a leaving group (LG, **18** to **19**, Scheme 1-8). Unfortunately, the tertiary centre in **18** is itself quite sterically demanding and hinders the approach of an incoming nucleophile. Consequently, these substitution reactions are difficult and often plagued by side reactions. One way to relieve this steric demand is to use a system where the nucleophile attacks a position remote from the centre bearing the leaving group. An example of such a reaction is the S$_N$2' reaction (**20** to **21**, Scheme 1-8). In addition to relieving unfavourable steric interactions, these S$_N$2' reactions are often highly stereoselective, allowing for the formation of stereogenic quaternary centres.



18 **19** **20** **21**

Scheme 1-8

Spino and Beaulieu used this strategy to generate stereogenic quaternary carbon centres from the S_N2' displacement of a chiral allylic pivalate with cyanocuprates (Table 1-4).[8] In this methodology, treatment of the chiral aldehyde **22**, available in two steps from commercial menthone, with vinylalane **23** leads to the allylic alcohol **24** with reasonable diastereoselectivity. Conversion of **24** to the corresponding pivalate followed by treatment with a cyanocuprate gives the product **25** in high yield and excellent stereoselectivity. Oxidation of the olefin in **25** allows for recovery of the chiral auxiliary and the formation of optically active acids **26** or aldehydes **27** bearing an α-quaternary carbon centre.

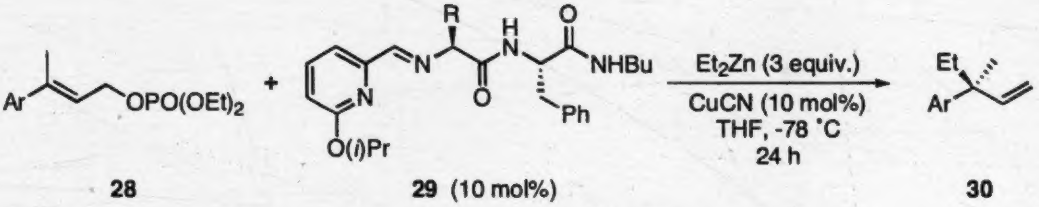


Entry	R^1	Yield of **24**	dr of **24**	R^2	Yield of **25**	de of **25**
1	(*c*)-Hex	75%	15:1	(*i*)-Pr	95%	>98%
2	$PhCH_2$	76%	12:1	(*i*)-Pr	92%	>98%
3	Ph	63%	20:1	(*i*)-Pr	90%	91%
5	$-(CH_2)_3OTBS$	68%	8:1	Et	89%	>98%
6	Bu	65%	13:1	C_7H_{15}	90%	>95%

Table 1-4. Stereogenic quaternary carbon centres from S_N2' addition of cyanocuprates to chiral allylic pivalates. TBS = (*t*)-Butyldimethylsilyl.

Although a good variety of groups may be used as R^1 and R^2, this reaction suffers in that the selectivity of the addition of the vinylalane **23** to aldehyde **24** is generally only moderate. Fortunately, the two isomers of the addition product **24** are readily separated by silica gel chromatography, allowing easy access to stereochemically pure allylic alcohol **24** for the subsequent cuprate displacement.

An enantioselective, catalytic version of this reaction has been developed by the Hoveyda group (Table 1-5).[9] In this process, substoichiometric amounts of a non-racemic peptide **29** and copper cyanide catalyse the allylic substitution of phosphonate esters **28** by alkylzinc reagents, yielding the olefin **30** in good yields and selectivities. Although the reaction is quite interesting and promising, the full scope and limitations have yet to be probed. Relatively few examples were reported and the selectivities, while promising, were on the low side.



Entry	Ar	R	Yield	ee (%)
1	C_6H_5	(*i*)-Pr	80	78
2	*o*-MeO-C_6H_4	(*c*)-Hex	70	78
3	*p*-NO_2-C_6H_4	(*t*)-Bu	80	86
4	*p*-TsO-C_6H_4	(*t*)-Bu	83	90
5	*p*-CF_3-C_6H_4	(*i*)-Pr	59	81

Table 1-5. Quaternary carbon centres from catalysed S_N2' cuprate additions.

1.3 Quaternary Carbon Centres via Carbonyl Allylation Chemistry

1.3.1 Introduction

Generating quaternary carbon centres though carbonyl allylation chemistry is an attractive strategy because of the very high levels of stereoselectivity that can be obtained in these reactions.[10] Furthermore, the products of these reactions, homoallylic alcohols, are quite useful reaction intermediates and are easily elaborated to more functionalized structures. Another benefit to this strategy is that many types allylation reactions can undergo enantioselective catalysis, which would allow for a very efficient generation of enantiopure quaternary carbon centres.

The success of a stereoselective allylation reaction depends strongly on the nature and reaction characteristics of the allylmetal in question. A classification system for allylation reagents that accounts for the different reaction mechanisms these reagents are generally accepted to follow has been proposed by Denmark and Weber (Figure 1-2).[11] According to this classification system, Type I reagents, exemplified by allylboron reagents, proceed via closed, Zimmerman-Traxler transition states, while Type II reagents (typified by most allyltin and allylsilicon reagents) go through open chain transition states.

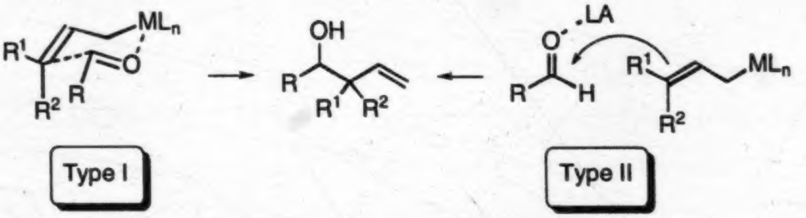


Figure 1-2. Type I and II allylation reagents.

Due to the compact, organized nature of the Zimmerman-Traxler transition state, allylations with γ-substituted Type I reagents generally show higher diastereoselectivities than reactions with the corresponding Type II reagents. Furthermore, the stereochemistry of the products of Type I allylations is readily and dependably predicted by these simple chair-like models, and generally *Z*-reagents lead to *syn* products and *E*-reagents to *anti* products. Conversely, Type II reagents generally operate through open chain transition states. Since a large number of possible open-chain transition states exist, diastereoselectivity with Type II reagents is not as reliable as with Type I reagents. As such, the stereochemistry of the products cannot be readily predicted by simple models. For example, reactions with many crotylstannanes are *stereoconvergent*, with both *E*- and *Z*-reagents yielding the same stereoisomer of the product (albeit with very different selectivities), while γ-disubstituted allylstannanes are *stereodivergent*, where the *E*- and *Z*-reagents yield opposite stereoisomers of the product (see below).

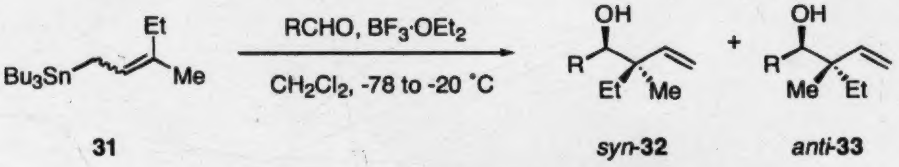
A second difference between Type I and II reagents is that the allylation reaction with Type I reagents is promoted by the internal coordination of the metal with the carbonyl of the aldehyde. In contrast, allylations with Type II reagents do not feature this internal coordination and consequently require activation with an external agent, typically a Lewis acid. Although the requirement for an external activator might appear to be a limitation, it has allowed for enantioselective additions through the use of chiral catalysts.

There have been several reports on the generation of stereogenic quaternary carbon centres from carbonyl allylation reactions. Those reactions involving allylstannanes and allylsilanes are discussed below. Since the use of allylboron reagents in this context is the subject of Chapter 3, a full discussion of these reagents will be left until then.

1.3.2 Quaternary carbon centres from allylstannation

Not much work has been done on the formation of quaternary carbon centres from γ-disubstituted allylstannanes. Perhaps this dearth of examples is due to the difficulty in preparing diastereomerically pure substituted allylstannanes, but it would appear to be more likely a result of the difficulty in controlling the relative stereochemistry of the products from allylstannations.[12] Diastereoselectivities observed with simple crotylstannanes, though often quite acceptable, vary dramatically depending on both the aldehyde and the choice of external activator.[13] If the relative stereochemistry of the addition cannot be adequately controlled, then the prospects for absolute control appear to be pretty dim. Correspondingly, most of the studies on catalytic enantioselective allylstannation have focussed on unsubstituted allylstannanes, where diastereoselectivity is not an issue. [14,15,16]

However, the use of disubstituted allylstannanes is not entirely unprecedented.[17] Surprisingly, the addition of diastereomerically pure 3-methyl-2-pentenylstannane **31** to aldehydes was found to be highly stereoselective (Table 1-6). Moreover, unlike additions of the corresponding crotylstannanes, the stereochemistry of the product alcohols **32** depended on the stereochemistry of the initial stannane, with the *E*-stannane yielding the *syn*-product and the *Z*-stannane leading to the *anti*-product **33**.[18]



Entry	R	Product Ratio *syn*-**32** : *anti*-**33**	
		From *E*-**31**	From *Z*-**31**
1	Ph	87:13	20:80
2	PhCH=CH	87:17	27:73
3	C_6H_{13}	98:2	7:93
4	*cyclo*-C_6H_{11}	>99:1	5:95

Table 1-6. Diastereoselective additions with γ-disubstituted allylstannanes **31**.

To explain this stereoselectivity, the authors propose that the reaction proceeds predominantly through a *syn*-synclinal transition state (Figure 1-3). They argue against a closed, Type I transition state, and suggest that the tin would not likely be able to compete with a strong Lewis acid like $BF_3 \cdot OEt_2$ for the carbonyl of the aldehyde. They also note that the products **32** and **33** have the opposite stereochemistry as that predicted by a cyclic transition state. However, the transfer of stereochemistry from the allylstannane **31** to the homoallylic alcohol **32** or **33** is not complete, and the level of stereoselectivity varies from one aldehyde to another. Both of these observations strongly suggest that additional transition states are operational in these allylstannations.

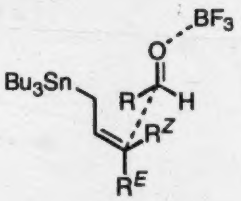
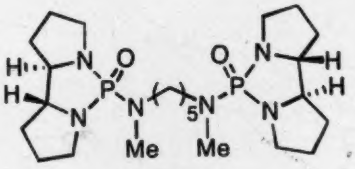


Figure 1-3. Proposed *syn*-synclinal transition state for allylstannations with **31**.

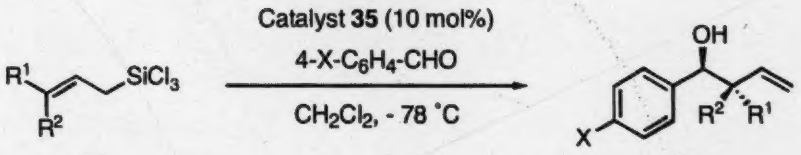
1.3.3 Quaternary carbon centres from allylsilation

Allylsilane reagents are approximately 10^3-10^4 times less reactive than the analogous allylstannanes.[10a] While thermal, uncatalysed reactions with allylstannanes are known, allylsilanes always require the presence of an external activator, usually a strong Lewis acid, before they can undergo an addition reaction.[12] One potential drawback to this requirement is that some substrates may not tolerate these conditions. Several alternate approaches to this activation problem have been reported recently,[19,20] but most have yet to show application to the generation of quaternary carbon centres.

A notable exception to this trend comes from Denmark and co-workers,[21] who exploit prior knowledge that some basic solvents (*e.g.*, DMF) are able to accelerate additions of allylic halosilanes.[22] Hexamethylphosphoramide (HMPA), even employed in substoichiometric amounts, was found to be an effective promoter and this strategy has now reached the stage where it can be successfully applied to absolute stereocontrol.[23] In the latest advance in this methodology, treatment of an allyltrichlorosilane **34** with a dimeric chiral phosphoramide catalyst **35** generates a highly reactive silane species which allylates aldehydes efficiently to give homoallylic alcohols **36** with high stereoselectivity (Table 1-7).[24]



(*R*, *R*) - **35**



34

36

Entry	Silane	Product	R^1	R^2	X	Yield (%)	ee (%)
1	**34a**	**36a**	H	H	H	85	87
2	**34b**	**36b**	H	H	MeO	84	88
3	**34c**	**36c**	H	H	CF_3	79	80
4	**34d**	**36d**	Me	H	H	82	86
5	**34e**	**36e**	H	Me	H	89	94
6	**34f**	**36f**	Me	Me	H	89	96
7	**34g**	**36g**	Ph	Me	H	64	94

Table 1-7. Catalytic enantioselective allylsilations with chiral bisphosphoramide **35**.

Under these conditions, unsaturated aldehydes react smoothly to give homoallylic alcohols **36** in good yields and high enantioselectivities. Enantiomeric excesses ranged from 80-95%, with electron-rich aldehydes (entry 2) tending to the higher end of this range and electron-poor (entry 3) to the lower. The high diastereoselectivity and the dependence of product stereochemistry on the geometry of γ-substituted silanes, as exemplified by the formation of **36d** and **36e**, show that these reagents display Type I behavior (entries 4 and 5). A significant extension of this work was demonstrated in a synthesis of the serotonin agonist LY426965, where the γ,γ-disubstituted silane **34g** underwent effective catalyzed addition to give key intermediate **36g** containing an enantioenriched quaternary carbon centre (entry 7).[25]

Mechanistically, the reaction is believed to proceed via a hexacoordinated silicon species (Figure 1-4).[26] Silicon has the ability to reach high coordination numbers (5 and 6) with different geometries and conformations.[27] Here, both phosphoramide groups of **35** chelate to the silicon, causing ionization by loss of a chloride anion. This ionization process generates a cationic, octahedral silane (**A**) which then undergoes reaction with the aldehyde via a chair-like Type I mechanism. The use of a bisphosphoramide ligand instead of a non-chelating monophosphoramide is essential in order to suppress competing pathways and obtain high enantioselectivities in the reaction. Chiral monophosphoramides also catalyse a selective reaction in an analogous manner to the bisphosphoramides, however, they also promote a less selective catalytic addition cycle via a pentacoordinate cationic silane (**B**) where only one phosphoramide binds to the silicon. Tethering the two phosphoramides together (*i.e.*, using a bisphosphoramide) effectively shuts down this competing process.

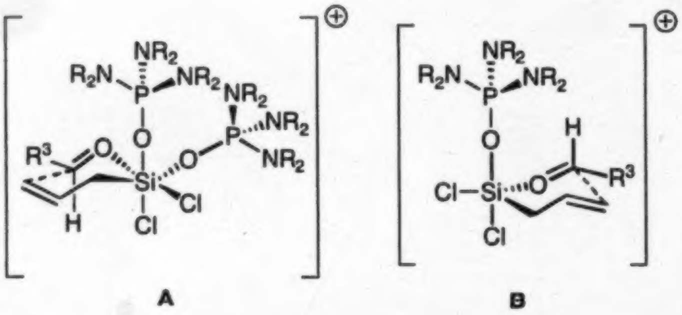
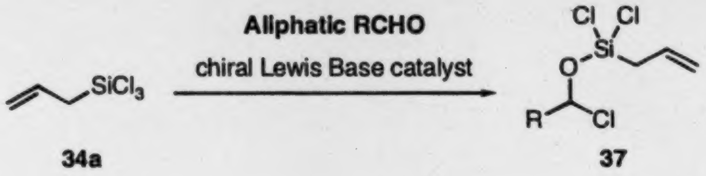


Figure 1-4. Proposed transition state structures in the addition of trichloroallylsilanes to aromatic and α,β-unsaturated aldehydes.[26]

A significant limitation to this approach is that it is currently not applicable to aliphatic aldehydes. Instead of producing the desired homoallylic alcohols, saturated aldehydes react with the liberated chloride anion to yield α-chloro silyl ethers **37** (Scheme 1-9). To date conditions have not been found that allow for the use of aliphatic substrates.



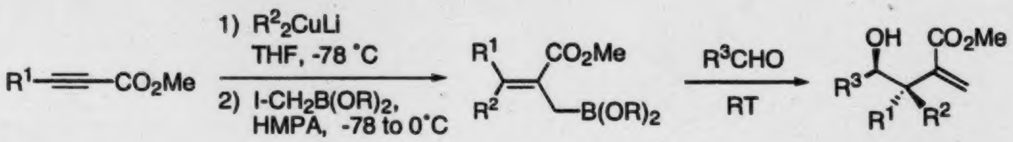
Scheme 1-9

1.4 Thesis Objective: Thermal and Catalysed Allylboration Strategies for the Preparation of Quaternary Carbon Centres

This thesis is concerned with the generation of quaternary carbon centres by the reaction of tetrasubstituted allylboronates **39** with aldehydes (Scheme 1-10). We believed that these Type I reagents would react efficiently with aldehydes to give homoallylic alcohols with the generation of a quaternary carbon centre. Furthermore, since allylboration reactions tend to show very high levels of diastereoselectivity, we expected the stereochemical information of the allylboronate **39** (*i.e.*, the *E*- or *Z*-stereochemistry of the olefin) to be transferred to the product. This expectation means that each isomer of **39** would lead to a different diastereomer of **40**, and thus either isomer of the quaternary centre could be produced by using the proper isomer of the allylboronate **39**. This versatility would make this strategy highly competitive with those described in Section 1.2. However, such a process depends on the availability of diastereomerically pure allylboronates **39**. Chapter 2 will describe how simple carbocupration of readily available alkynoate esters **38** allows for the convenient preparation of these compounds with excellent control of the olefin geometry.

Chapter 3 concerns the preparation of diastereomerically and enantiomerically pure quaternary carbon centres by the thermal reaction of these tetrasubstituted allylboronates **39** with aldehydes. Although quite effective, one unfortunate drawback to this chemistry is that the thermal allylation reaction with these boronates was found to be quite slow. In order to increase the efficiency of the overall sequence and to potentially investigate enantioselective additions, we sought to develop a catalytic version. Over the course of these studies, we were pleased to find that allylborations can be effectively catalysed by mild Lewis acids.

The catalysis observed is significant – reactions that previously took over 10 days to reach completion are now completed within 12 hours. Furthermore, this catalytic effect appears to occur without disrupting the important Type I mechanism and the stereospecificity observed in the thermal allylborations. Chapter 4 will describe the development and optimization of this novel catalytic allylation methodology in detail.



38 **39** **40**

Thermal Reaction: 2 weeks
With 10% metal triflate: 12 h

Scheme 1-10

1.5 References

(1) (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419-460; (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037-2066; (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401; (d) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591-4597.

(2) (a) Mulzer, J.; Dürner, G.; Trauner, D. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2830-2832; (b) Christoffers, J.; Rößler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701-705; (c) Christoffers, J.; Mann, A. *Chem. Eur. J.* **2001**, *7*, 1014-1027; (d) Enders, D.; Teschner, P.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2001**, 4463-4477; (e) Christoffers, J.; Baro, A.; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688-1690.

(3) Fukuda, Y.-i.; Sasaki, H.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2002**, *43*, 2047-2049.

(4) Enders, D.; Knopp, M.; Runsink, J.; Raabe, G. *Liebigs Ann.* **1996**, 1095-1116.

(5) For a review, see Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503-9569.

(6) (a) Enders, D.; Zamponi, A.; Raabe, G.; Runsink, J. *Synthesis* **1993**, 725-728; (b) Enders, D.; Zamponi, A.; Schäfer, T.; Nübling, C.; Eichenauer, H.; Demir, A. S.; Raabe, G. *Chem. Ber.* **1994**, *127*, 1707-1721.

(7) (a) Manthorpe, J. M.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 2338-2341; (b) Manthorpe, J. M.; Gleason, J. L *J. Am. Chem. Soc.* **2001**, *123*, 2091-2092.

(8) Spino, C.; Beaulieu, C. *Angew. Chem. Int. Ed.* **2000**, *39*, 1930-1932.

(9) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1456-1460.

(10) (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2001**, pp 299-401; (b) Hoppe, D; Roush, W. R.; Thomas, E. J. In *Stereoselective Synthesis: Methods of Organic Chemistry (Houben-Weyl), 4th Ed*; Helmchen. G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, **1995**; Vol. E21b, pp 1257-1602; (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207-2293; (d) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555-566.

(11) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655-1660.

(12) For a review, see Thomas, E. J., in reference 10b, pp 1508-1540.

(13) (a) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889-7896 and references therein; (b) For a recent example, see Nishigaichi, Y.; Takuwa, A. *Tetrahedron Lett.* **2003**, *44*, 1405-1408.

(14) For reactions with aldehydes, see Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897-7900. See also citations in references 15b and 16.

(15) For reactions with ketones, see: (a) Cunningham, A.; Woodward, S. *Synlett* **2002** 43-44; (b) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061-1063.

(16) For a study with crotylstannanes, see Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 4381-4384.

(17) Nishigaichi, Y.; Takuwa, A. *Tetrahedron Lett.* **1999**, *40*, 109-112.

(18) Here *syn* and *anti* refer to the relative configuration of the OH group in **32** or **33** and the group that had priority in the allylstannane. In the case of **31**, that group would be the ethyl group.

(19) For a review, see Kennedy, J. W. J.; Hall, D. G. *Angew. Chem. Int. Ed.* **2003**, *in press.*

(20) For a recent example, see Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *in press.*

(21) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167-170.

(22) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453-3456. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620-6628.

(23) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161-6163.

(24) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488-9489.

(25) Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951-1953.

(26) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021-12022.

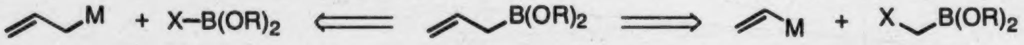
(27) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371-1448.

Chapter 2

Preparation of Tetrasubstituted Allylboronates

2.1 Introduction

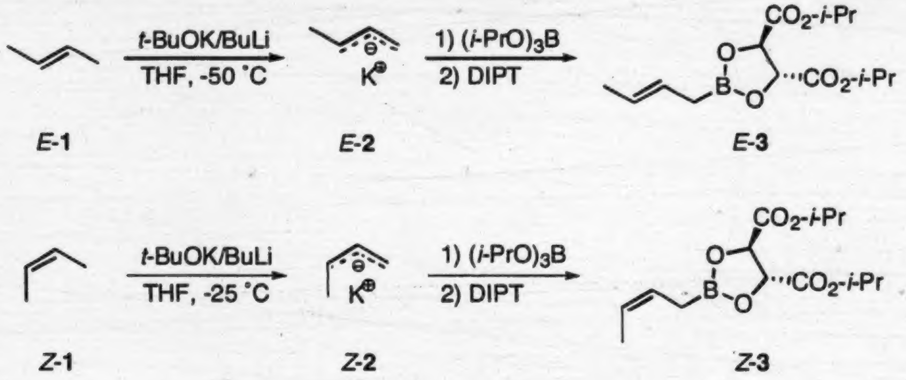
As part of our ultimate goal to prepare stereogenic quaternary carbon centres, we needed a reliable route to stereodefined, γ-disubstituted allylboronates. Although there were several known preparative routes to allylboronates,[1] we felt that none of them could be used for our purposes. Conceptually, allylboronates can be prepared by quenching either an allylmetal or an alkenylmetal species with an appropriate boron-containing electrophile (Scheme 2-1). Both of these routes are discussed below, but generally the two differ in that the yields are greater from the reaction of allylmetals but stereoselectivity is better via the alkenylmetal route. In light of the numerous reviews on the preparation of allylboronates,[1] the discussion below will focus mainly on preparations that are pertinent to this thesis. However, some new methods for the preparation of allylboronates that are not mentioned in these reviews will also be presented.



Scheme 2-1

2.1.1 Allylboronates from allylmetal intermediates

As mentioned above, one route to allylboronates is the quenching of reactive allylmetals with boronic esters. Roush and co-workers opted to use this approach to prepare tartrate modified crotyl boronates **3** from the corresponding crotylpotassiums **2** (Scheme 2-2).[2] Though quite effective in these simple cases, we did not expect to be able to prepare stereodefined γ-disubstituted compound via this route. The biggest problem that we anticipated was that many allylmetals are configurationally unstable.[3] While simple allyl and crotyl derivatives can be prepared with good control of the olefin geometry, we anticipated that more elaborately substituted derivatives would not lead to stereopure compounds. Another problem was that the conditions to prepare these allylmetals are quite harsh and might lead to incompatibilities with many functional groups.

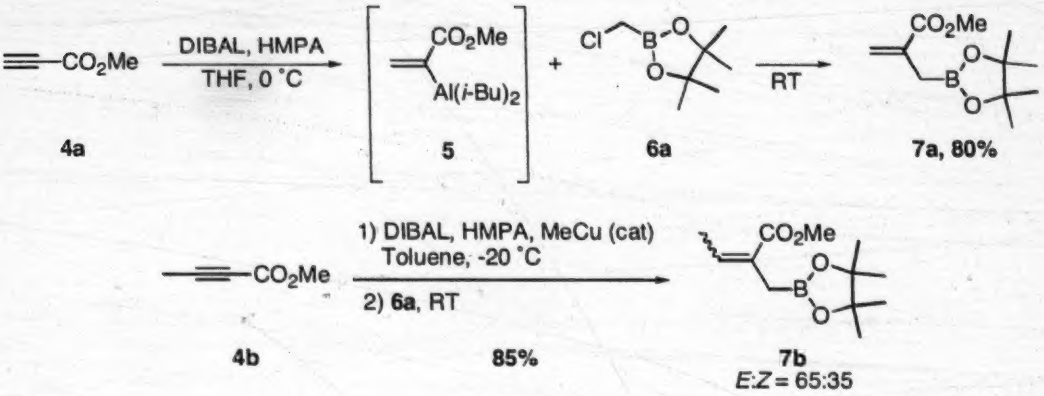


Scheme 2-2

2.1.2 Allylboronates from alkenylmetal intermediates

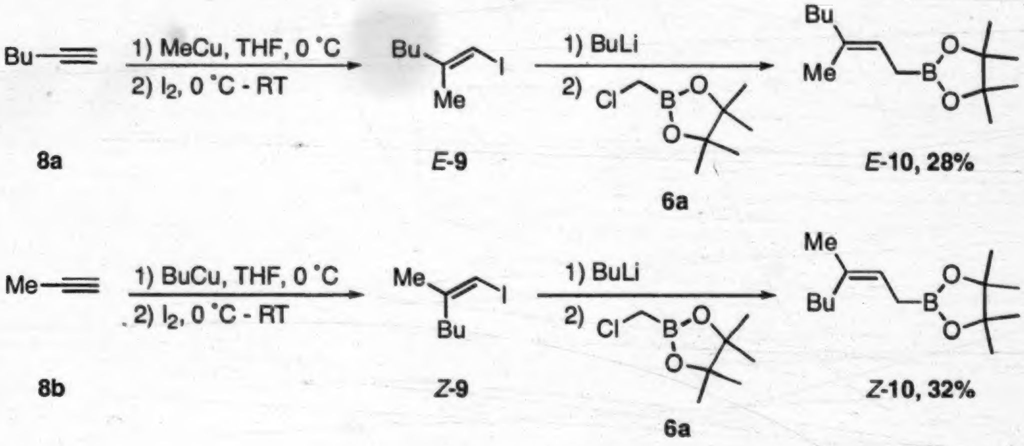
A more promising approach to γ-disubstituted allylboronates is via the reaction of an alkenylmetal anion with a halomethaneboronate. Alkenylmetal reagents are generally more configurationally stable than allylmetals and so alkylations with these anions are usually more stereoselective than with allyl anions. However, the low reactivity of many alkenylmetals can sometimes bring about poor yields in the alkylation. While the reaction of alkenyllithium and alkenylmagnesium reagents with halomethaneboronates is well established,[4] the high reactivity of these organometallics limits the number of functional groups that may be present.

The Villiéras group has used hydroalumination chemistry to generate 2-carbomethoxyallylboronates **7** from alkynoate esters **4** and chloromethaneboronate **6a** via alkenylaluminum **5** (Scheme 2-3).[5] Though promising, this route suffered from some limitations, mainly in that it could not be extended to γ-substituted allylboronates since the hydroalumination of internal alkynoates did not proceed with good *E*:*Z* selectivity.[6] Another limitation is that the alumination of alkynes is currently limited to the transfer of either hydrogen or methyl groups.[7]



Scheme 2-3

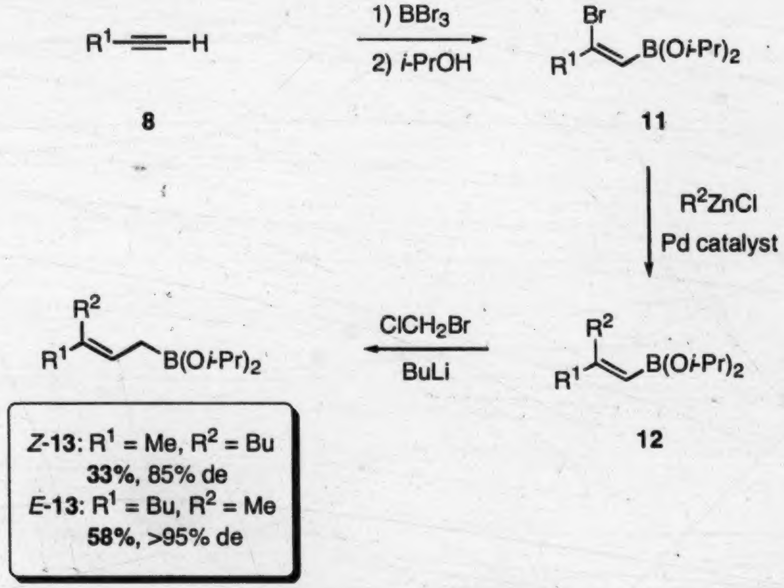
Hoffmann and Schlapbach reported the preparation of both isomers of the γ-disubstituted allylboronate **10** via the geometrically pure alkenyllithiums generated from alkenyliodides **9**, which were in turn prepared from the carbocupration of the terminal alkynes **8** (Scheme 2-4).[8] Although effective for the preparation both *E*- and *Z*-isomers of the substituted allylboronate **10**, this route suffered from two drawbacks. First, it is a two-step procedure and the overall low yield of the sequence reflects the cumbersome copper to iodine to lithium exchange. Secondly, the intermediacy of an alkenyllithium limits the number of functional groups that can be present on the final allylboronate.



Scheme 2-4

Sato and co-workers published a different route to these γ-disubstituted allylboronates (Scheme 2-5).[9] Here, bromoboration of terminal acetylenes **8** followed by

Negishi coupling[10] and Matteson homologation[11] gave access to diastereomerically pure **13**. Although this route is longer than the preceding one, the overall yields of allylboronate **13** were generally higher in this protocol compared to the carbocupration route. Like Hoffmann and Schlapbach's preparation, both of the R groups are introduced independently and with high stereoselectivity, which makes both *E*- and *Z*-isomers of **13** available from this sequence.

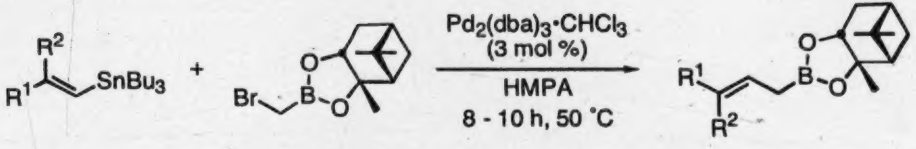


Scheme 2-5

2.1.3 Non-traditional preparations of allylboronates

2.1.3.1 Allylboronates from palladium cross-coupling reactions

Although the preparation of allylboronates by Negishi coupling reactions has been known since the early 1990's,[12,13] the corresponding Stille process has only recently been reported.[14] Nevertheless, bromomethaneboronate **15** couples with a variety of alkenylstannanes **14** under palladium catalysis to give boronate **16** (Table 2-1). These couplings proceed with retention of olefin stereochemistry (entries 4 and 5) and the reaction tolerates a wide range of functional groups.

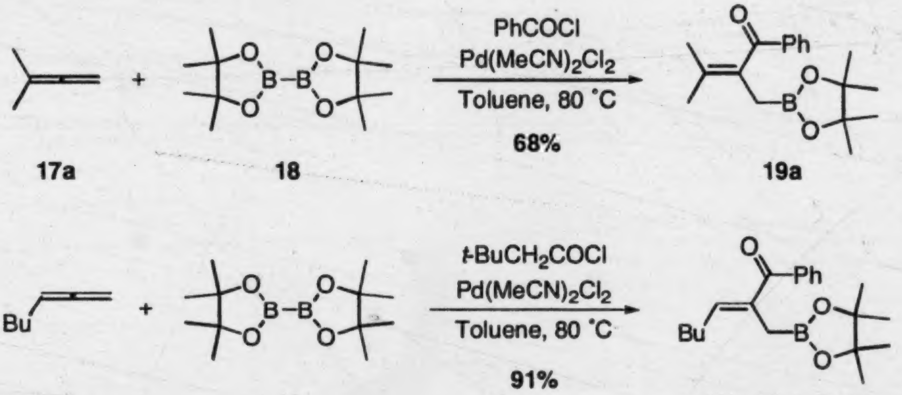


14 **15** **16**

Entry	R^1	R^2	Yield (%)
1	$Ph(CH_2)_3$-	H	80
2	$MeO_2C(CH_2)_3$-	H	78
3	$NC(CH_2)_3$-	H	76
4	Ph	H	60
5	H	Ph	60

Table 2-1. Allylboronates **16** from Stille cross-coupling.

Cheng and co-workers reported a novel route to tetrasubstituted allylboronates from allenes **17** and diboron compounds **18** that proceeds via a palladium-allyl complex (Scheme 2-6).[15] This route allows for the preparation of a wide variety of highly substituted allylboronates with excellent levels of stereoselectivity. Unfortunately, the stereoselectivity derives from the relative sizes of the two groups at the terminus of the allene, and thus only *gem*-dimethyl tetrasubstituted allylboronates (*e.g.*, **19a**, where there is no difference in the groups) and *E*-trisubstituted allylboronates (*e.g.*, **19b**, where the difference is very large) have been prepared using this chemistry. Surprisingly, the reaction of these allylboronates with aldehydes has not yet been reported.



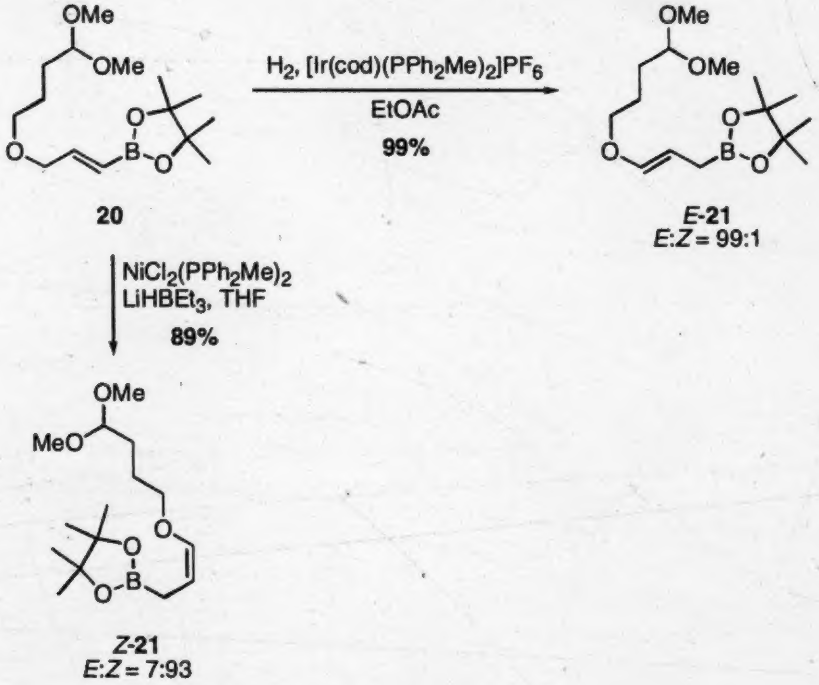
17a **18** **19a**

17b **18** **19b**, 99:1 *E*: Z

Scheme 2-6

2.1.3.2 *Allylboronates by transition metal catalysed double bond migration*

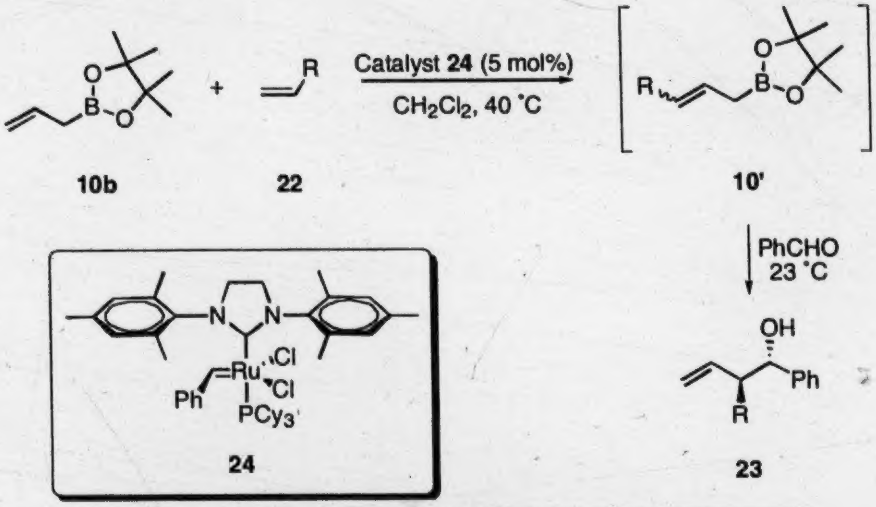
Some transition metals are able to isomerize an alkenylboronate **20** to the corresponding allylboronate **21** by double bond migration (Scheme 2-7).[16] This process was developed in order to prepare stereochemically pure *E*-γ-alkoxyallylboronates *E*-**21**, compounds which are difficult to access by the usual methods described above. These reagents are available by the iridium catalysed isomerization of the alkenylboronate **20** to give *E*-**21** with excellent selectivity. Use of a nickel catalyst instead of iridium allows for access to the opposite isomer, *Z*-**21**, albeit in slightly lower selectivity.



Scheme 2-7

2.1.3.3 *Allylboronates by olefin cross-metathesis*

In contrast to the preparative methods described above, the olefin metathesis route followed by Goldberg and Grubbs creates a functionalized allylboronate from a simpler allylboronate (Table 2-2).[17] Here, treatment of pinacol allylboronate **10b** with a variety of olefin metathesis partners **22** in the presence of catalyst **24** smoothly leads to formation of a more elaborate allylboronate, the cross product **10'**. This new boronate is not isolated but rather is treated directly with benzaldehyde to give the homoallylic products **23** in good yield.



10b **22** **10'** **24** **23**

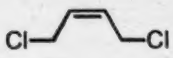
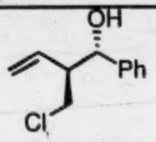
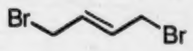
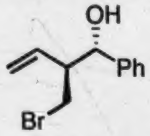
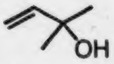
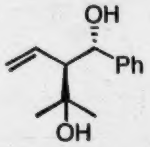
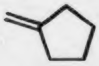
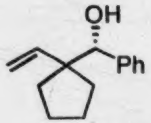
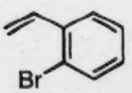
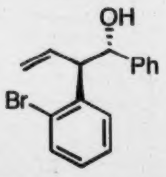
Entry	Cross Partner **22**	Product **23**	Yield (%)	dr
1			73	3.8:1
2			78	4.9:1
3			58	>20 : 1
4			66	>20 : 1
5			60	>20 : 1

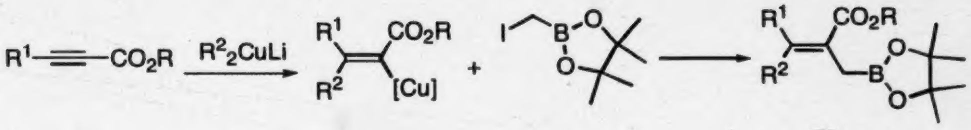
Table 2-2. Allylboronates from olefin cross metathesis.

The main advantage that this route has over others is that it is exceptionally tolerant of sensitive functional groups. Entry 3 shows an example with an unprotected alcohol, and entries 1, 2, and 5 all show examples of halogenated groups that were delivered directly from an allylboronate. These groups, which would not have survived the strongly basic conditions or the active metals used in the other preparations, are carried through this procedure without incident. Entry 4 is also noteworthy because it shows that quaternary carbon centres can be made with this chemistry.

A serious limitation with this preparation is that the diastereoselectivity seen in the formation of **23** is quite variable. Although olefin cross partners **22** with large allylic substituents (*e.g.*, entries 3-5) react to give exclusively the *anti*-**23** shown in Table 2-2, olefins with smaller substituents (entries 1 and 2) show a much lower preference. Furthermore, both *E* and *Z* olefins afford the same stereoisomer of alcohol **23** (compare entries 1 and 2).

2.1.4 Our approach: Tetrasubstituted allylboronates from alkenylcuprates

Similar to the work of Schlapbach and Hoffmann,[8] we decided to explore a route to tetrasubstituted allylboronates starting from the carbocupration of alkynoate esters (Scheme 2-8). However, we sought to achieve a more convenient, and hopefully higher yielding, one-pot procedure. Here, treatment of the alkynoate ester **4** with a dialkylcuprate would yield alkenylcopper intermediate **25** which would subsequently be trapped by iodomethaneboronate **6b** to give the tetrasubstituted boronate **26**. We were inspired to explore this route because the carbocupration of alkynoate esters is known to proceed stereospecifically to give one isomer of the alkenylcopper species **25**.[18] Another attractive feature of this strategy is that a large number of alkynoate esters and cuprates are available, which allows for a wide variety of R groups in the products. However, this alkenylcopper intermediate is notoriously unreactive and is typically only trapped by very active electrophiles.[19] At the outset of these studies, we wondered if electrophile **6b** would be sufficiently reactive to trap this intermediate, or, if not, whether we could find conditions that would allow for effective trapping. We were also aware that the 2-carboalkoxyalkenylcopper intermediate **25** is configurationally unstable at temperatures above -30 °C,[20] and any alkylation conditions would have to contend with this potential pitfall.



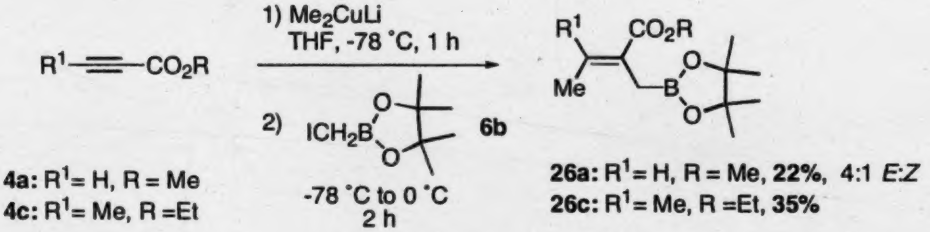
4 **25** **6b** **26**

Scheme 2-8

2.2 Results

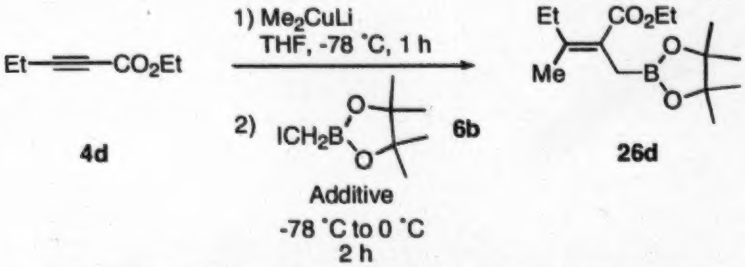
2.2.1 Diastereoselective preparation of tetrasubstituted allylboronates 26

Our initial experiments following the procedure of Hall and co-workers[19b] yielded promising, if somewhat modest, results. Thus, methyl propionate **4a** and ethyl 2-butynoate **4c** were both successfully converted into their respective allylboronates **26a** and **26c** (Scheme 2-9). Unfortunately, the yields for both compounds were not good and the *E*:*Z* selectivity for **26a** was low.



Scheme 2-9

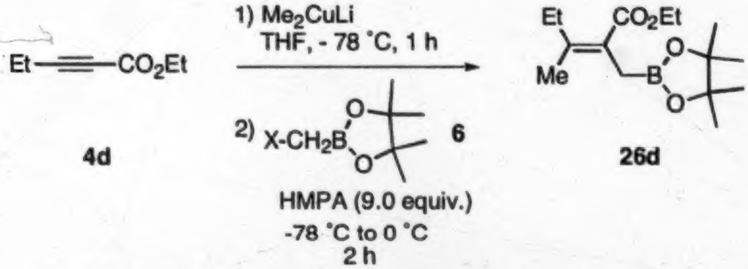
A breakthrough came when we discovered that adding hexamethylphosphoramide (HMPA) to the electrophilic quench allowed for the formation of tetrasubstituted allylboronates **26** in good yield and excellent diastereoselectivity (Table 2-3). The data show that at least 9 equivalents of HMPA are required to achieve a highly selective reaction (entry 1), and that selectivity erodes as the amount of HMPA is decreased (entries 2 and 3). Attempts were then made to find a replacement for the carcinogenic HMPA. Unfortunately, no other additive tried to date rivals HMPA in its efficiency at providing good yields of highly stereopure products. Although DMPU comes the closest, it must be used in much larger amounts in order to achieve the same results (entry 4).



Entry	Additive	Equivalents	Yield (%)	*E* : *Z* Selectivity
1	HMPA	9	68	1 : 17
2	HMPA	3	(100)	1 : 12
3	HMPA	1	(100)	1 : 4
4	DMPU	43[a]	(69)	1 : >20
5	DMPU	9	34	1 : 10
6	DMPU	3	(81)	1 : 8
7	DMPU	1	(99)	1 : 1
8	DMEU	9	54	1 : 12
9	TMEDA	7	0	-

Table 2-3. Additive study. Reactions done on 1 mmol scale in 5 mL of THF. *E*:*Z* ratio determined by ^{1}H NMR of the crude reaction mixture. Yields in brackets are from unpurified products. [a] DMPU used as a 1:1 co-solvent with THF.

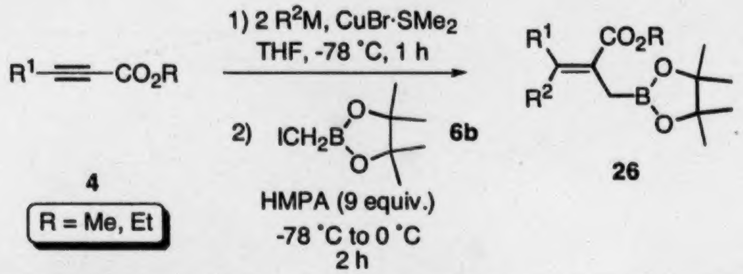
Finally, we determined that the iodomethaneboronate **6b** is a more effective electrophile in the alkylation step than the chloro analogue **6a** (Table 2-4).[21]



Entry	Electrophile	X	Yield of **26d** (%)	*E* : *Z* ratio
1	**6a**	Cl	38	1: 2
2	**6b**	I	66	1 : >20

Table 2-4. Effect of different electrophiles.

Now that we had established an effective protocol, we set out to explore the scope of the kinds of boronates that could be prepared. We were pleased to find that a large number of tetrasubstituted allylboronates could be prepared using this convenient, one-pot, two-step procedure (Table 2-5).[22] Initially we did not know how stable the boronates **26** were, and consequently some of the yields below are compiled from crude products. We eventually found that these boronates are in fact quite robust, and could be readily purified by flash chromatography.



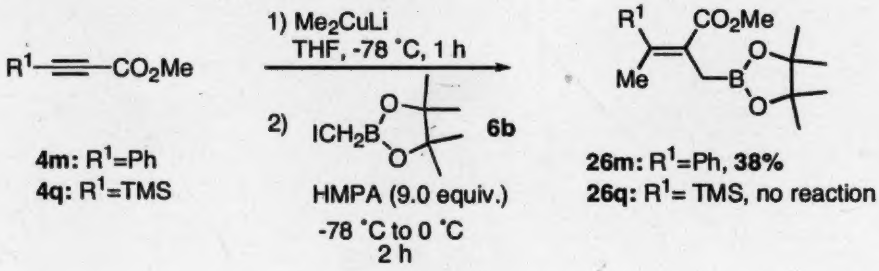
Entry	Alkynoate	Boronate	R^1	R^{2}M	Yield	*E*:*Z*
1[a]	**4a**	**26a**	H	MeLi	60%	>20 : 1
2	**4c**	**26c**	Me	MeLi	(99%)	-
3	**4d**	**26d**	Et	MeLi	68%	1 : 17
4	**4e**	**26e**	Bu	MeLi	(99%)	1 : >20
5	**4f**	**26f**	Me	BuLi	78%	>20 : 1
6	**4g**	**26g**	Me	(*i*)-BuMgCl	45%	>20 : 1
7	**4h**	**26h**	Me	(*s*)-BuLi	58%	>20 : 1
8	**4i**	**26i**	Me	(*t*)-BuLi	72%	2:1
9[a]	**4j**	**26j**	Et	BuLi	60%	>20 : 1
10	**4k**	**26k**	Bu	OctylMgCl	24%	>20 : 1
11	**4l**	**26l**	Me	AllylMgCl	60%	19 : 1
12	**4m**	**26m**	Ph	MeLi	38%	1 : >20
13	**4n**	**26n**	TPSOCH$_2$-	MeLi	60%	1 : >20
14	**4o**	**26o**	TPSO(CH$_2$)$_2$-	MeLi	(92%)	1 : >20
15	**4p**	**26p**	Me	TMS(CH$_2$)$_2$OCH$_2$Li	28%	>20 : 1

Table 2-5. Yields and diastereomeric ratios of prepared allylboronates **26**. Yields in brackets are for crude products, others are of compounds purified by flash chromatography. TPS = *tert*-Butyldiphenylsilyl. [a] Boronate prepared by the alternative preparation. See Section 2.2.2 below.

As can be seen from Table 2-5, cuprates derived from alkyllithium and Grignard reagents may be used. Branched organometallic reagents are also effective in the reaction, though the stereoselectivity of the product decreases for extremely demanding reagents (*c.f.*, entries 5, 7 and 8). Unsaturation may be present in the cuprate as long as the unsaturation is not directly next to the copper. Thus, allyl groups are effectively transferred (entry 12), but not vinyl and phenyl groups In these cases, the major product is the protonated olefin, suggesting that the problem originates in the electrophilic quench. A single, low yielding example was obtained with a cuprate bearing a protected alcohol (Entry 15).

Likewise, there are few limitations on the kind of alkynoate that may be used in this reaction. Alkynoates that were not commercial are readily prepared by the reaction of terminal alkynes with methyl chloroformate.[23] So far, alkynoates where the R group has been a primary aliphatic chain have been used, as well as alkynoates bearing protected alcohols (entries 13 and 14). Overall, these results show that this procedure is able to produce highly functionalized allylboronates, compounds which could eventually find application in natural product synthesis.

Two substrates that did not perform well in the reaction are shown in Scheme 2-10. Methyl 3-phenylpropiolate **4m** gave only a low yield of boronate **26m** along with significant amounts of unreacted alkynoate, and the TMS-protected **4q** was recovered unchanged after reaction. Performing the 1,4-addition of these substrates at a higher temperature (-40 °C) did not improve the outcome.



Scheme 2-10

The stereochemistry of the products was determined by analysis of the ^{1}H NMR spectrum. In all cases, the *Z*-substituent (which is *cis* to the ester group) was found downfield from the *E*-substituent, presumably due to anisotropic deshielding from the ester. This deshielding of the *Z*-substituent has been noted before.[19] ^{1}H nOe experiments on boronate **26d** ($CDCl_3$, 300 MHz) were consistent with the proposed structure (Figure 2-1). Irradiation at the Z-CH_2 group caused enhancement of the signals for the two groups of protons on the ethyl ester but not of the signal for the CH_2-B protons. Unfortunately, the chemical shift of the *E*-methyl group (δ 1.73 ppm) was too close to that of the methylene adjacent to the boron (δ 1.82 ppm) to allow for selective irradiation.

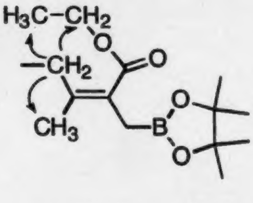
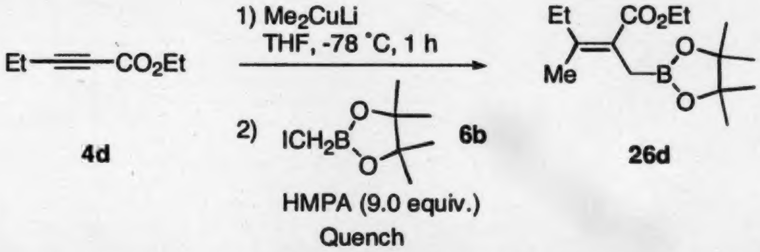


Figure 2-1. nOe enhancements observed with boronate **26d** upon irradiation of the *Z*-CH_2 protons.

2.2.2 Alternative preparation of tetrasubstituted allylboronates 26

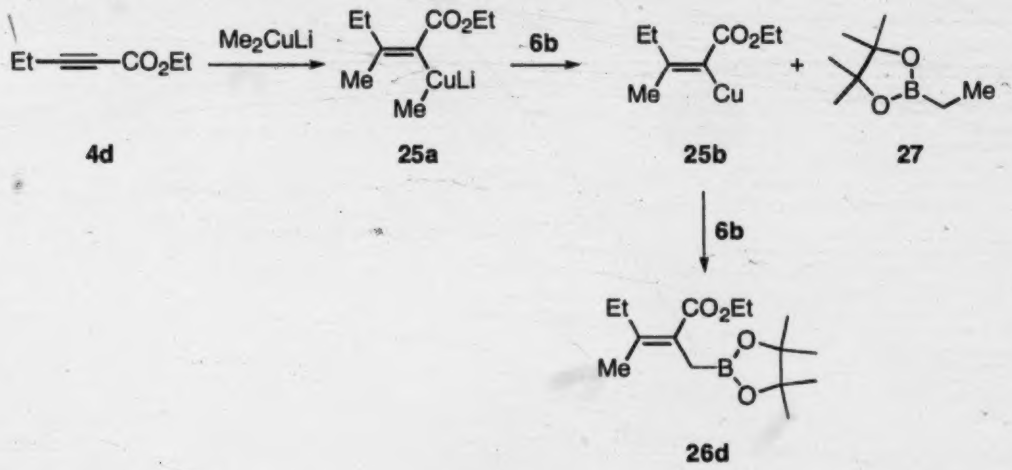
The major problem with the sequence described above was the use of three equivalents of electrophile **6b** in the alkylation step. Although the preparation of **6b** is not difficult, a more efficient process would obviously be useful.[24] We found that yields and selectivities using only two equivalents of **6b** were comparable to those obtained when three equivalents are employed as long as the electrophilic quench was performed at room temperature (Table 2-6, entry 3).



Entry	Equivalents of **6b**	Quench Conditions	Yield	*E* : *Z* Selectivity
1	1	0 °C, 4h	0	-
2	2	0 °C, 4h	27	1 : >20
3	2	RT, 2h	53	1 : >20
4	3	0 °C, 2h	66	1 : >20
5	4	0 °C, 3h	72	1 : >20

Table 2-6. Optimization of the preparation of **24d** for equivalents of **6b** and temperature.

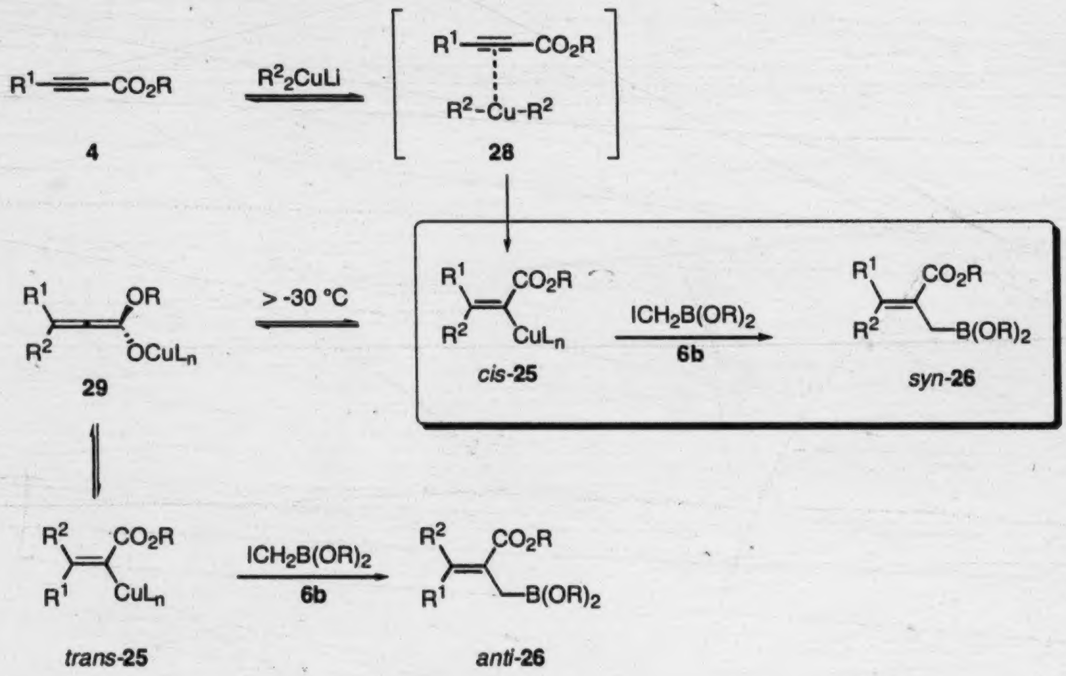
Interestingly, no boronate was formed at all if only one equivalent of **6b** was used (entry 1). This result suggests that the first equivalent of iodomethaneboronate **6b** is consumed by preferential transfer of the methyl group over the alkenyl group from the mixed cuprate **25a** to the electrophile **6b** (Scheme 2-11). Selectivity in the transfer of ligands in unsymmetrical cuprates has long been an issue in organocopper chemistry, and saturated ligands are generally transferred faster in substitution reactions than unsaturated ligands.[25] Although this problem might be circumvented by using a cuprate bearing a non-transferable group, none have yet been probed for use in this reaction.[26]



Scheme 2-11

2.2.3 Reaction mechanism and the role of the additive

A brief outline of the course of the reaction is shown in Scheme 2-12.[20,27] The reaction of alkynoates with organocuprates was long postulated to proceed via a π-complex **28** followed by initial formation of alkenylcopper species *cis*-**25**, possibly via a copper(III) intermediate. While this high-oxidation state copper(III) intermediate has not yet been experimentally observed, low temperature NMR studies have confirmed that the π-complex **28** forms prior to formation of *cis*-**25**. A consequence of the intermediacy of the π-complex is that the R group and the Cu are both transferred to the same face of the alkyne, resulting in overall *syn* addition.



Scheme 2-12

From here, alkylation of intermediate *cis*-**25** with iodomethaneboronate **6b** would lead to the desired *syn*-**26**, the product from overall *syn* addition of the cuprate and the electrophile. However, there is a competing process where the alkenylcopper intermediate *cis*-**25** can isomerize to *trans*-**25** via allenoate **29**. Alkylation of this intermediate would then lead to the undesired stereoisomer *anti*-**26**. The success of the reaction hinges on the successful alkylation of *cis*-**25** under conditions that inhibit this isomerization process.

From the first reports of this reaction, it was known that overall *syn* selectivity is higher when the reaction is performed in THF rather than ether.[18] Klein and Levene found that excess MeLi in the reaction mixture causes loss of stereoselectivity in the addition.[28] Recent low temperature NMR studies established that lithium facilitates the equilibrium and this observation suggests that the reaction is more selective in THF because this solvent is more effective at sequestering lithium from the reaction medium than diethyl ether.[27] Temperature also affects the rate of isomerization of *cis*-**25**, and even in THF, the reaction must be kept quite cold (generally below -30 °C) in order to prevent isomerization. Unfortunately, effective alkylation of **25** with unactivated electrophiles does not occur at these temperatures.[19a]

However, in the presence of certain additives the selective alkylation of *cis*-**25** is possible. There are two possible roles for the additive in this reaction. It might enhance the alkylation step sufficiently so that reaction can occur at temperatures which prohibit isomerization of the alkenylcopper intermediate. Conversely, it may help to stabilize the alkenylcopper by sequestering lithium from the reaction so that isomerization does not occur at the warmer temperatures required for the alkylation. Following a systematic study of various additives,[29] we now believe that HMPA is the most effective of the additives tested because it can perform both of these roles. HMPA is roughly 300 times more effective than THF at sequestering lithium,[30] and so one would expect that HMPA would be more effective at suppressing isomerization of the alkenylcopper **25** than THF alone. However, effective removal of lithium is not sufficient to allow for a successful alkylation. Reaction using 12-crown-4, a very effective lithium chelating agent, instead of HMPA leads to selective formation of *syn*-**26** but in low yield.[29] Therefore, HMPA must also enhance the alkylation step, an ability that has been documented previously.[31] DMPU has been used as an effective substitute for the carcinogenic HMPA, and previous studies[32] show that the same beneficial effects of HMPA can be obtained with this cyclic urea if it is used in double the amount of HMPA. The results obtained in this thesis are in line with these literature precedents.

2.3 Experimental

2.3.1 General

Methyl 2-heptynoate **4e**,[34b] methyl 3-phenylpropynoate **4m**,[34b] methyl 4-(*tert*-butyldiphenylsilyloxy)-2-butynoate **4n**,[33,34] methyl 5-(*tert*-butyldiphenylsilyloxy)-2-pentynoate **4o**,[34] and iodomethaneboronate **6b**[24] were prepared by literature procedures. Tetrahydrofuran was distilled from sodium-benzophenone. HMPA and DMPU were distilled over CaH_2 before use. Alkyllithiums were titrated according to the Gilman double titration method[35] prior to use. All other chemicals were purchased from either the Aldrich Chemical Company or Caledon Chemicals and used as received. Glassware for cuprate reactions was flame-dried under vacuum and then allowed to cool under an inert atmosphere. $NH_4Cl_{(aq)}$ and $NaHCO_{3(aq)}$ refer to saturated aqueous solutions. Thin layer chromatography data was performed on Merck Silica Gel 60 F_{254} plates and were visualized with UV light and either 5% phosphomolybdic acid in ethanol (PMA) or 1% $KMnO_{4(aq)}$. R_f values are approximate. NMR spectra were recorded on Bruker AM 300, Bruker AM 200, Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$ and were performed in quartz NMR tubes. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab.

2.3.2 Boronates 26 from 3 equivalents of electrophile 6b

2.3.2.1 *Ethyl 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoate 26c*

A slurry of $CuBr \cdot SMe_2$ (1.35 g, 6.58 mmol) in THF (15 mL) at 0 °C under Ar was treated with MeLi (1.18 M in ether, 11.2 mL, 13.2 mmol). When the clear, colourless solution had formed (~10 min) the flask was placed in an acetone/CO_2 bath and treated via canula with a –78 °C solution of ethyl 2-butynoate (0.721 g, 6.43 mmol) in THF (2.5 mL + 2.5 mL canula rinse). The resulting light brown mixture was stirred at –78 °C for 1 h and then injected sequentially with iodomethaneboronate **6b** (4.85 g, 18.10 mmol) and DMPU (15 mL). After 10 minutes the mixture was brought to 0 °C, left to stir for 2 h, and then the reaction was quenched with $NH_4Cl_{(aq)}$ (25 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 25 mL). The combined organic layers were washed with water (6 x 25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated to give the product as a yellow oil (1.554 g, 90%).

TLC (25% Et_2O/Hexane, $KMnO_4$): 0.36; ^1H NMR (300 MHz, $CDCl_3$): δ 4.14 (q, J = 7.1 Hz, 2H), 2.06 (s, 3H), 1.86 (s, 2H), 1.77 (s, 3H), 1.26 (t, J =7.1 Hz, 3H), 1.22 (s, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.4, 142.4, 123.7, 83.1, 59.9, 24.7, 23.0, 14.3; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.7; IR (CH_2Cl_2 cast, cm^{-1}): 2979, 1713, 1635, 1148; HRMS (EI, *m/z*) Calcd for $C_{14}H_{25}{}^{11}BO_4$: 268.18460. Found: 268.18450.

2.3.2.2 *Ethyl (2Z)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylpent-2-enoate 26d*

A slurry of $CuBr\cdot SMe_2$ (1.11 g, 5.39 mmol) in THF (7.5 mL) at 0 °C under Ar was treated with MeLi (1.27 M in Et_2O, 8.6 mL, 11 mmol). When the clear, colourless solution had formed (~10 min) the flask was placed in an acetone/CO_2 bath and treated via canula with a –78 °C solution of ethyl 2-pentynoate (674 mg, 5.34 mmol) in THF (2.5 mL + 2.5 mL canula rinse). The resulting light brown mixture was stirred at –78 °C for 1 h and then injected sequentially with iodomethaneboronate **6b** (3.700 mg, 13.81 mmol) and HMPA (7.5 mL). After 10 minutes the mixture was brought to 0 °C, left to stir for 2 h, and then reaction was quenched with $NH_4Cl_{(aq)}$ (25 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 25 mL). The combined organic layers were washed with water (6 x 25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated to give the product as a yellow oil (1.090 g, 3.834 mmol, 72%). The product was purified by Kugelrohr distillation (0.1 torr, 200 °C) to give a colourless oil (1.020 g, 3.614 mmol, 68%). TLC (25% Et_2O/Hexane, $KMnO_4$): 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13 (q, *J* = 7.1 Hz, 2H), 2.36 (q, *J* = 7.4, 2H), 1.82 (s, 2H), 1.75 (s, 3H), 1.26 (t, *J* = 7.1, 3H), 1.21 (s, 12H), 1.02 (t, *J* = 7.4, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.2, 147.1, 123.3, 83.0, 59.8, 29.5, 24.6, 20.2, 14.2, 12.8; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.7, 22.3 (impurity); IR (CH_2Cl_2 cast, cm^{-1}): 2978, 1713, 1633, 1147; HRMS (EI, *m/z*) Calcd for $C_{15}H_{27}{}^{11}BO_4$: 282.20023. Found: 282.20020.

2.3.2.3 *Methyl (2Z)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylhept-2-enoate 26e*

This compound was prepared according to the procedure in Section 2.3.2.2, with $CuBr\cdot SMe_2$ (225 mg, 1.01 mmol), MeLi (1.47 M in ether, 1.5 mL, 2.2 mmol), methyl 2-heptynoate **4e** (156 mg, 1.12 mmol) and iodomethaneboronate **6b** (0.5 mL, 3 mmol) using DMPU (5 mL) instead of HMPA to give the desired boronate as a yellow oil (251 mg, 85%).

TLC (25% Et_2O/Hexane, $KMnO_4$): 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 2.41 (d, *J* = 8 Hz, 2H), 1.84 (s, 2H), 1.79 (s, 3H), 1.41 (m, 2H), 1.32 (m, 2H), 1.25 (m, 12H + impurities), 0.90 (t, *J* = 4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.9, 146.9, 123.4, 83.1, 51.0, 36.1, 30.6, 24.6, 22.6, 20.9, 15.0, 14.0; ^{11}B NMR (128 MHz, $CDCl_3$): δ 34.0, 22.3 (impurity); IR (CH_2Cl_2 cast, cm^{-1}): 2978, 1718, 1629, 1109; HRMS (EI, *m/z*) Calcd for $C_{16}H_{29}{}^{11}BO_4$: 296.21588. Found: 296.21643.

2.3.2.4 *Ethyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylhept-2-enoate 26f*

The dibutylcuprate was formed by adding *n*-BuLi (1.6 M in Hexanes, 1.3 mL, 2.1 mmol) to a slurry of CuBr·SMe$_2$ (207 mg, 1.00 mmol) in THF (3 mL) at –40 °C. After the dark brown homogenous solution formed (~30 min), the preparation was carried out as described in Section 2.3.2.2, with ethyl 2-butynoate (130 mg, 1.16 mmol) and iodomethaneboronate **6b** (807 mg, 3.01 mmol). The desired boronate was obtained as a yellow oil (466 mg, >100%).

^{1}H NMR (300 MHz, CDCl$_3$): δ 4.18 (q, *J* = 6 Hz, 2H), 2.09 (m, 2H), 2.01 (s, 3H), 1.86 (s, 2H), 1.38 (m, 2H), 1.24 (m, 12H + impurities), 0.89 (m, 3H + hydrocarbon impurities); ^{13}C NMR (75 MHz, CDCl$_3$): δ 169.5, 146.4, 123.5, 83.1, 59.9, 36.8, 29.6, 24.6, 22.9, 21.2, 14.3, 14.0; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.3, 22.0 (impurity); IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2978, 1714, 1627, 1148; HRMS (EI, *m/z*) Calcd for $C_{17}H_{31}{}^{11}BO_4$: 310.23154. Found: 310.23185.

2.3.2.5 *Ethyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,5-dimethylhex-2-enoate 26g*

The dibutylcuprate was formed by adding isobutylmagnesium chloride (2.0 M in THF, 1.1 mL, 2.2 mmol) to a slurry of CuBr·SMe$_2$ (222 mg, 1.08 mmol) in THF (1.5 mL) at –40 °C. After a black mixture formed (~30 min), the preparation was carried out described in Section 2.3.2.2, with ethyl 2-butynoate (121 mg, 1.08 mmol) and iodomethaneboronate **6b** (0.96 g, 3.6 mmol). The product was then purified by flash chromatography (25% Et$_2$O/Hexanes, 23 g silica) to give the desired boronate (149 mg, 0.481 mmol, 44%).

TLC (25% Et$_2$O/Hexane, KMnO$_4$): 0.48; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.15 (q, *J* = 7.1 Hz, 2H), 2.02 (d, *J* = 7.3 Hz, 2H), 2.00 (s, 3H), 1.90 (br s, 2H) 1.86 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 12H), 0.89 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 169.5, 145.2, 124.7, 83.1, 59.9, 45.6, 27.2, 24.7, 22.6, 21.7; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.6; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2977, 1715, 1624, 1349, 1148; HRMS (EI, *m/z*) Calcd for $C_{17}H_{31}{}^{11}BO_4$: 310.23154. Found: 310.23236.

2.3.2.6 *Ethyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4-dimethylhex-2-enoate 26g*

The dibutylcuprate was formed by adding (*s*)-BuLi (1.40 M in cyclohexane, 1.6 mL, 2.2 mmol) to a slurry of CuBr·SMe$_2$ (226 mg, 1.10 mmol) in THF (1 mL) at –40 °C. After a black mixture formed (~30 min), the preparation was carried out as described in Section 2.3.2.2, with ethyl 2-butynoate (117 mg, 1.04 mmol) and iodomethaneboronate **6b** (1.06 g, 3.94 mmol). The product was then purified by Kugelrohr distillation (175 °C, 0.1 torr) to give the desired boronate (219 mg, 0.706 mmol, 70%).

TLC (25% Et$_2$O/Hexane, KMnO$_4$): 0.50; ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.14 (q, *J* = 7.0 Hz, 2H), 2.54 (m, 1H), 1.90 (d, *J* = 3.4 Hz, 2H), 1.82 (t, *J* = 1 Hz, 3H), 1.36 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 12H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.7, 148.0, 123.5, 83.0, 59.8, 38.7, 27.4, 24.8, 24.7, 18.0, 14.5, 14.3, 12.2; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.7; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2976, 1713, 1616, 1146; HRMS (EI, *m/z*) Calcd for C$_{17}$H$_{31}$^{11}BO$_4$: 310.23154. Found: 310.23180.

2.3.2.7 *Ethyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,4,4-trimethylpent-2-enoate 26i*

The dibutylcuprate was formed by adding (*t*)-BuLi (1.54 M in pentane, 1.3 mL, 2.0 mmol) to a slurry of CuBr·SMe$_2$ (203 mg, 0.989 mmol) in THF (1 mL) at –40 °C. After a black mixture formed (~60 min), the preparation was carried out as described in Section 2.3.2.2, with ethyl 2-butynoate (110 mg, 0.986 mmol) and iodomethaneboronate **6b** (911 g, 3.41 mmol). The product was then purified by silica gel chromatography (25% Et$_2$O/Hexane) to give the desired boronate as a colourless oil (222 mg, 0.714 mmol, 72%) as a 2:1 mixture of diastereomers.

TLC (25% Et$_2$O/Hexane, KMnO$_4$): 0.38; ^{1}H NMR (500 MHz, CDCl$_3$): Major Isomer: δ 4.16 (q, *J* = 7.2 Hz, 2H), 2.06 (br s, 2H), 1.79 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.21 (s, 12H), 1.17 (s, 9H); Minor Isomer: δ 4.12 (q, *J* = 7.2 Hz, 2H), 1.77 (br s, 2H), 1.65 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.21 (s, 12H), 1.09 (s, 9H); ^{13}C NMR[a] (125 MHz, CDCl$_3$): δ 173.3, 172.2, 145.1, 140.6, 126.1, 122.8, 83.2, 83.1, 60.1, 37.3, 36.3, 30.0, 29.4, 24.8, 24.7, 19.8, 16.6, 14.0; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.1; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2978, 1720, 1610, 1341, 1143; HRMS (EI, *m/z*) Calcd for C$_{17}$H$_{31}$^{11}BO$_4$: 310.23154. Found: 310.23241.

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[a] The ^{13}C resonances for the two isomers of the boronate **26i** were not assigned.

2.3.2.8 Methyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-butylundec-2-enoate 26k

The dioctylcuprate was formed by adding octylmagnesium chloride (2.0 M in THF, 1.1 mL, 2.2 mmol) to a slurry of CuBr·SMe$_2$ (228 mg, 1.11 mmol) in THF (3.0 mL) at 0 °C. After a purple mixture formed (~2 min), flask was immersed in a –78 °C bath and the preparation was carried out as described in Section 2.3.2.2, with methyl 2-heptynoate **4e** (154 mg, 1.10 mmol) and iodomethaneboronate **6b** (0.97 g, 3.6 mmol). The product was then purified by flash chromatography (10% Et$_2$O/Hexanes, 22 g silica) to give the desired boronate that show some hydrocarbon impurities (104 mg, 0.264 mmol, 24%).

TLC (10% Et$_2$O/Hexane, KMnO$_4$): 0.29; ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.65 (s, 3H), 2.35 (m, 2H), 2.06 (m, 2H), 1.81 (s, 2H), 1.44-1.18 (m, 16 H), 1.20 (s, 12H), 0.87 (m,6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.4, 151.4, 123.2, 83.0, 51.0, 34.7, 34.3, 31.9, 31.2, 30.1, 29.6, 29.3, 27.9, 24.7, 23.0, 22.7, 14.1, 14.0; ^{11}B NMR (128 MHz, CDCl$_3$): δ 32.7; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2927, 1720, 1623, 1348, 1147; HRMS (EI, *m/z*) Calcd for $C_{23}H_{43}{}^{11}BO_4$: 394.32544. Found: 394.32545.

2.3.2.9 Methyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylhexa-2,5-dienoate 26l

The cuprate was formed by adding allylmagnesium chloride (2.0 M in THF, 1.0 mL, 2.0 mmol) to a slurry of CuBr·SMe$_2$ (209 mg, 1.02 mmol) in THF (3 mL) at –40 °C. After a tan mixture formed (~30 min), the preparation was carried out as described in Section 2.3.2.2, with methyl 2-butynoate (99 mg, 1.0 mmol) and iodomethaneboronate **6b** (0.83 g, 3.1 mmol). The product was then purified by flash chromatography (25% Et$_2$O/Hexanes, 30 g silica) to give the desired boronate (170 mg, 0.606 mmol, 60%).

TLC (25% Et$_2$O/Hexane, KMnO$_4$): 0.48; ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.74 (m, 1H), 5.03 (m, 2H), 3.68 (s, 3H), 2.86 (d, 2H), 2.01 (s, 3H), 1.87 (br s, 2H), 1.20 (s, 12H).; ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.3, 143.5, 133.9, 124.6, 116.1, 83.1, 51.1, 40.9, 24.7, 21.1; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.8;IR (CH$_2$Cl$_2$ cast, cm^{-1}): 3078, 2978, 1719, 1631, 1349, 1146, 993, 914; HRMS (EI, *m/z*) Calcd for $C_{15}H_{25}{}^{11}BO_4$: 280.18460. Found: 280.18496.

2.3.2.10 *Methyl (2E)-3-Phenyl-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate 26m*

This compound was prepared according to the procedure in Section 2.3.2.2, with CuBr·SMe$_2$ (242 mg, 1.18 mmol), MeLi (1.27 M in ether, 1.8 mL, 2.3 mmol), methyl 3-phenylpropynoate **4m** (182 mg, 1.14 mmol) and iodomethaneboronate **6b** (865 mg, 3.23 mmol) to give the crude boronate as an oil (244 mg). Purification by flash chromatography (25% Et$_2$O/Hexane, 15 g silica) gave the desired boronate which contained some aromatic impurities (125 mg, 0.394 mmol, 35%).

TLC (25% Et$_2$O/Hexane, KMnO$_4$): 0.38; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.3-7.0 (m, 5H), 3.35 (s, 3H), 2.07 (s, 3H), 2.00 (s, 2H), 1.24 (s, 12H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.3, 144.3, 142.5, 127.7, 126.8, 126.5, 125.3, 83.2, 51.0, 24.8, 22.3; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2978, 1709, 1631, 1598, 1346, 1109, 765, 701; HRMS (EI, *m/z*) Calcd for C$_{18}$H$_{25}$^{11}BO$_4$: 316.18460. Found: 316.18460.

2.3.2.11 *Methyl (2Z)-4-(tert-butyldiphenylsilyloxy)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoate 26n*

This compound was prepared according to the procedure in Section 2.3.2.2, with CuBr·SMe$_2$ (210 mg, 1.02 mmol), MeLi (1.27 M in ether, 1.6 mL, 2.0 mmol), methyl 4-(*tert*-butyldiphenylsilyloxy)-2-butynoate **4n** (368 mg, 1.01 mmol) and iodomethaneboronate **6b** (846 mg, 3.16 mmol) to give the crude boronate as an oil (556 mg). Purification by flash chromatography (25% Et$_2$O/Hexane, 27 g silica) gave the desired boronate (308 mg, 0.606 mmol, 60%).

TLC (25% Et$_2$O/Hexane, KMnO$_4$): 0.41; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.64 (m, 4H), 7.37 (m, 6H), 4.58 (s, 2H), 3.47 (s, 3H), 1.94 (s, 3H), 1.86 (s, 2H), 1.21 (s, 12H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 168.6, 145.6, 135.5, 133.7, 129.4, 127.7, 127.5, 124.3, 83.2, 65.2, 51.2, 27.0, 24.9, 19.5, 17.2; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.2; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 3071, 2856, 1715, 1634, 1589, 1347, 1112, 1070, 741, 702; HRMS (ES, *m/z*) Calcd for C$_{29}$H$_{41}$^{11}BSiO$_5$Na: 531.271403. Found: 531.270743.

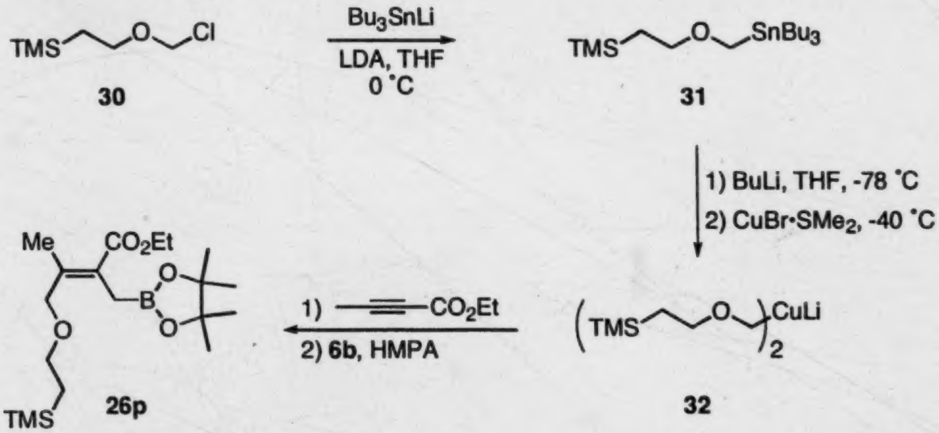
2.3.2.12 *Methyl (2Z)-5-(tert-butyldiphenylsilyloxy)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylpent-2-enoate 26o*

This compound was prepared according to the procedure in Section 2.3.2.2, with CuBr·SMe$_2$ (221 mg, 1.07 mmol), MeLi (1.27 M in ether, 1.7 mL, 2.1 mmol), methyl

5-(*tert*-butyldiphenylsilyloxy)-2-pentynoate **4o** (404 mg, 1.06 mmol) and iodomethaneboronate **6b** (752 mg, 2.81 mmol) to give the crude boronate as an oil (487 mg, 92%).

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.64 (m, 4H), 7.36 (m, 6H), 3.77 (d, J = 6.3 Hz, 2H), 3.61 (s, 3H), 2.73 (d, J = 6.3 Hz, 2H), 1.84 (s, 2H), 1.76 (s, 3H), 1.19 (s, 12H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.0, 143.9, 135.5, 133.9, 129.4, 127.5, 125.2, 83.1, 63.3, 51.1, 39.5, 27.0, 24.9, 24.8, 19.3; ^{11}B NMR (64 MHz, CDCl$_3$): δ 33.4; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 3070, 2931, 1718, 1622, 1589, 1348, 1146, 1111, 739, 702; HRMS (EI, *m/z*) Calcd for C$_{29}$H$_{40}$^{11}BSiO$_4$ (M$^+$ - (*t*)-Bu): 491.27890. Found: 491.27823.

2.3.2.13 *Ethyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3,5-dimethylhex-2-enoate 26p*



Stannane **31**:[36] A solution of diisopropylamine (2.0 mL, 14 mmol) in THF (25 mL) at 0 °C was treated with BuLi (1.65 M, 7.5 mL, 12 mmol), stirred for 10 min and then treated dropwise with freshly distilled Bu$_3$SnH (3.37 g, 11.6 mmol) and left to stir at this temperature. After 20 minutes, the resulting yellow solution was treated dropwise with SEM-Cl **30** (5.04 g, 30.2 mmol), stirred for 5 minutes, and then poured into a mixture of hexane (200 mL) and 1 M HCl/brine (100 mL). The layers were separated and the organic layer was washed with 5% NaHCO$_{3(aq)}$, dried (MgSO$_4$) and concentrated to give the crude product. Distillation (0.1 torr, 150 °C bath) gave stannane **31** as a colourless oil (bp = 135 °C, 3.60 g, 8.54 mmol, 74%). ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.68 (m, $J_{\text{Sn-H}}$ = 6.8 Hz, 2H), 3.36 (m, 2H), 1.49 (m, 6H), 1.28 (m, 6H), 0.88 (m, 17H), -0.02 (s, 9H).

The cuprate **32** was prepared in analogy to the procedure of Overman and Paone.[37] A flame dried flask under Ar was charged with a stir bar and CuBr·SMe_2 (262 mg, 1.27 mmol) and immersed in a –78 °C bath. In a second flask, a solution of stannane **31** (1.02 g, 2.53 mmol) in THF (3.8 mL) under Ar was chilled to –78 °C and treated with BuLi (1.65 M, 1.5 mL, 2.5 mmol). After 15 min this solution was transferred via canula to the flask containing CuBr·SMe_2. The resulting pink mixture was then stirred at –40 °C for 1 h, causing a black mixture of the cuprate **30** to form. This mixture was then brought back to –78 °C, and the boronate **26p** was prepared as described in Section 2.3.2.2, with ethyl 2-butynoate (146 mg, 1.30 mmol) and iodomethaneboronate **6b** (0.75 mL, 3.9 mmol). The product was purified by flash chromatography (25% Et_2O/Hexanes, 91 g silica) to give the desired boronate (134 mg, 0.348 mmol, 28%).

TLC (25% Et_2O/Hexane, $KMnO_4$): 0.28; ^1H NMR (500 MHz, $CDCl_3$): δ 4.16 (q, *J* = 7.2 Hz, 2H), 3.98 (s. 3H), 3.45 (m, 2H), 2.02 (s, 3H), 1.90 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 12H), 0.92 (m, 2H), -0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 141.2, 126.3, 83.1, 71.2, 67.5, 60.0, 24.6, 18.22, 18.20, 14.2, -1.4; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.7; IR (CH_2Cl_2 cast, cm^{-1}): 2978, 1717, 1632, 1349, 1146; HRMS (EI, *m/z*) Calcd for $C_{19}H_{37}{}^{11}BSiO_5$: 384.25034. Found: 384.25140.

2.3.3 Boronates 26 from 2 equivalents of electrophile 6b

2.3.3.1 Methyl (2E)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-but-2-enoate 26a

A slurry of CuBr·SMe_2 (211 mg, 1.03 mmol) in THF (3 mL) at 0 °C under Ar was treated with MeLi (1.45 M in Et_2O, 1.4 mL, 2.0 mmol). When the clear, colourless solution had formed (~10 min) the flask was placed in an acetone/CO_2 bath and treated via canula with a –78 °C solution of methyl propiolate (86 mg, 1.02 mmol) in THF (0.5 mL + 0.5 mL canula rinse). The resulting light brown mixture was stirred at –78 °C for 1 h and then injected sequentially with iodomethaneboronate **6b** (0.66 g, 2.5 mmol) and HMPA (1.8 mL, 10 mmol). After 5 minutes the mixture was brought to RT, left to stir for 2 h, and then the reaction was quenched with $NH_4Cl_{(aq)}$ (10 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 10 mL). The combined organic layers were washed with water (6 x 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated, yielding a yellow oil (254 mg). Flash chromatography (25% Et_2O/Hexanes, 15 g SiO_2) gave the product as a colourless oil (140 mg, 0.611 mmol, 60%).

TLC (25% Et_2O/Hexane, $KMnO_4$): 0.31; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (qt, J = 7.0 Hz, 1.1 Hz, 1H), 3.68 (s, 3H), 1.83 (br s, 2H), 1.75 (dt, J = 7.0 Hz, 0.8 Hz, 3H), 1.21 (s, 12 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.3, 135.5, 129.9, 83.2, 51.5, 24.7, 14.5; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.6; IR (CH_2Cl_2 cast, cm^{-1}): 2978, 1712, 1651, 1145, 756; HRMS (EI, *m/z*) Calcd for $C_{12}H_{21}{}^{11}BO_4$: 240.15329. Found: 240.15289.

2.3.3.2 *Methyl (2Z)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-ethylhept-2-enoate 26j*

A slurry of CuBr·SMe_2 (966.4 mg, 4.70 mmol) in THF (15 mL) at 0 °C under Ar was treated with BuLi (1.60 M in Hexanes, 5.8 mL, 9.3 mmol). After 5 minutes, the dark mixture was placed in an acetone/CO_2 bath and treated via canula with a –78 °C solution of ethyl 2-pentynoate (592 mg, 4.69 mmol) in THF (2.5 mL + 2.5 mL canula rinse). The resulting light brown mixture was stirred at –78 °C for 1 h and then injected sequentially with iodomethaneboronate **6b** (2.57 g, 9.59 mmol) and HMPA (7.5 mL, 43 mmol). After 5 minutes the mixture was brought to RT, left to stir for 2 h, and then reaction was quenched with $NH_4Cl_{(aq)}$ (25 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 25 mL). The combined organic layers were washed with water (6 x 25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated, yielding a yellow oil (254 mg). Flash chromatography (25% Et_2O/Hexanes, 114 g SiO_2) gave the product as a colourless oil (0.91 g, 2.80 mmol, 60%).

TLC (25% Et_2O/Hexane, $KMnO_4$): 0.44; ^{1}H NMR (500 MHz, $CDCl_3$): 4.13 (q, J = 7.1 Hz, 2H), 2.36 (q, J = 7.4 Hz, 2H), 2.07 (m, 2H), 1.83 (br s, 2H), 1.42-1.38 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.20 (s, 12H), 1.02 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 151.6, 123.3, 82.9, 59.7, 33.7, 30.0, 27.4, 24.7, 23.0, 14.2, 13.9, 13.3; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.9; IR (CH_2Cl_2 cast, cm^{-1}): 2977, 1714, 1625, 1348, 1147; HRMS (EI, *m/z*) Calcd for $C_{18}H_{33}{}^{11}BO_4$: 324.24719. Found: 324.24757.

2.4 References

(1) (a) Matteson, D. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin Heidelberg, **1995**; 260-328; (b) Roush, W. R. In *Stereoselective Synthesis: Methods of Organic Chemistry (Houben-Weyl), 4th Ed.;* Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, **1995**; Vol. E21b, pp 1410-1486.

(2) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.

(3) Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555-642.

(4) (a) Brown, H. C.; De Lue, N. R.; Yamamoto, Y.; Maruyama, K.; Kasahara, T.; Murahashi, S.-i.; Sonoda, A. *J. Org. Chem.* **1977**, *42*, 4088-4092; (b) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, *122*, 1783-1789.

(5) Nyzam, V.; Belaud, C.; Villiéras, J. *Tetrahedron Lett.* **1993**, *34*, 6899-6902.

(6) Nyzam, V.; Ph. D. Thesis, Université de Nantes, France, **1996**.

(7) (a) Van Horn, D. E.; Negishi, E.-i *J. Am. Chem. Soc.* **1978**, *100*, 2252-2254; (b) Negishi, E.-i.; Van Horn D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639-6647.

(8) Hoffmann, R. W.; Schlapbach, A. *Liebigs. Ann. Chem.* **1990**, 1243-1248.

(9) Sato, M.; Yamamoto, Y.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7071-7074.

(10) Negishi, E.-i.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298-3299.

(11) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631-632 and references therein.

(12) Hoffmann, R. W.; Sander, T.; Hense, A. *Liebigs Ann. Chem.* **1993**, 771-775.

(13) Watanabe, T.; Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1993**, *444*, C1-C3.

(14) Falck, J. R.; Bondlela, M.; Ye, J. H.; Cho, S. D. *Tetrahedron Lett.* **1999**, *40*, 5647-5650.

(15) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2000**, *122*, 7122-7123.

(16) (a) Yamamoto, Y.; Kurihara, K.; Yamada, A.; Takahashi, M.; Takahashi, Y.; Miyaura, N. *Tetrahedron* **2003**, *59*, 537-542; (b) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413-416.

(17) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 807-810.

(18) (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851-1852; (b) Siddall, J. B.; Biskup, M.; Fried, J. H. *ibid.* 1853-1854.

(19) (a) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621-4628; (b) Hall, D. G.; Chapdelaine, D.; Préville, P.; Deslongchamps, P. *Synlett* **1994**, 660-662.

(20) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051-2058.

(21) Chloromethaneboronate **6a** can be prepared by: Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137-141.

(22) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898-899.

(23) Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058-2064.

(24) Of the numerous preparations of iodomethaneboronate **6b** available, the one that we found to be the most convenient on large scale was: Phillion, D. P.; Neubauer, R.; Andrew, S. S. *J. Org. Chem.* **1986**, *51*, 1610-1612. For alternative preparations, see references 11 and 21.

(25) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. A. *J. Org. Chem.* **1984**, *49*, 3928-3938.

(26) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437-447.

(27) Nilsson, K.; Ullenius, C.; Krause, N. *J. Am. Chem. Soc.* **1996**, *118*, 4194-4195.

(28) Klein, J.; Levene, R. *Perkin Trans. II* **1973**, 1971-1978.

(29) Zhu, N.; Hall, D. G. *J. Org. Chem.* **2003**, *in press*.

(30) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527-6535.

(31) (a) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, 826-830; (b) Piers, E.; Chong, J. M.; Keay, B. A. *Tetrahedron Lett.* **1985**, *26*, 6265-6268; (c) Ando, K.; Takemasa, Y.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 1579-1588.

(32) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385-391 and references therein.

(33) Zacharie, B.; Gagnon, L.; Attardo, G.; Connolly, T. P.; St-Denis, Y.; Penney, C. L. *J. Med. Chem.* **1997**, *40*, 2883-2894.

(34) (a) Nagaoka, H.; Kishi, Y. *Tetrahedron*, **1981**, *37*, 3873; (b) Hall, D. G.; Ph. D. Thesis, Université de Sherbrooke, **1995**, p. 257.

(35) Taylor, R. K.; Casy, G. In *Organocopper Reagents : A Practical Approach;* Taylor, R. K., Ed.; Oxford University Press: New York, **1994**, pp 53-72.

(36) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481-1486; (b) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930-4939; (c) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1989**, *8*, 1593-1598.

(37) Overman, L.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465-9467.

Chapter 3

Stereogenic Quaternary Carbon Centres from Tetrasubstituted Allylboronates

3.1 Introduction

In this work, we sought to explore an efficient route to stereogenic quaternary carbon centres through allylboration chemistry because allylboronates are well known to undergo highly diastereoselective reactions with aldehydes. The additions of unsubstituted and γ-monosubstituted allylboronates, especially the crotylboronates **1**, have been extensively studied.[1] These reactions are thought to proceed via the Type I mechanism, namely a compact, 6-membered, chair-like transition state (Figure 3-1). The stereochemistry of the products of these additions is readily and reliably predicted from these simple models. Furthermore, enantioselective variants of this reaction are known, and allow for the efficient, enantioselective construction of secondary and tertiary carbon centres.[2]

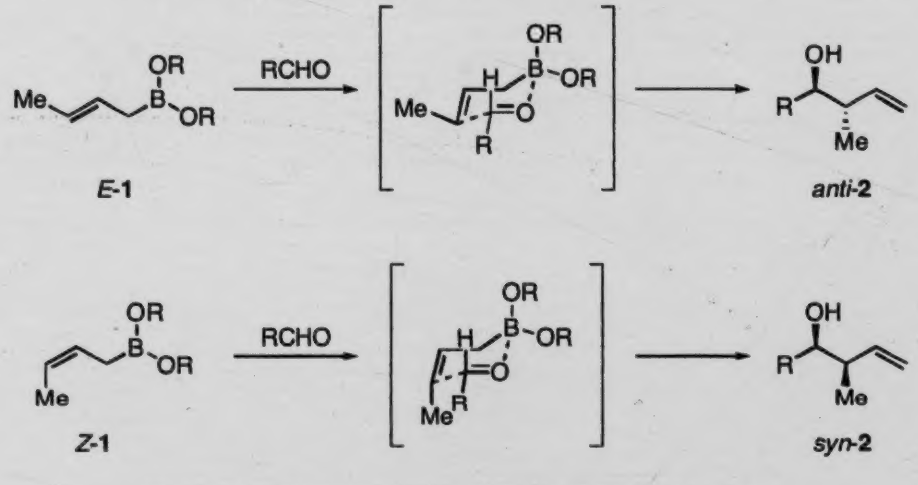
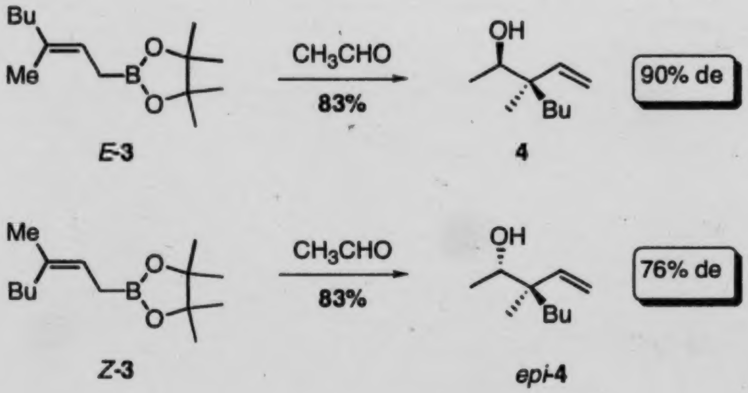


Figure 3-1. Diastereoselective additions with crotylboronates.

Although γ-disubstituted allylboronates are similarly quite selective in their reactions, very few examples of their use in the generation of quaternary carbon centres have been shown. Presumably this omission is due to the difficulty in preparing diastereomerically pure γ-disubstituted allylboronates However, since we had developed a practical route to these compounds, we were now in a position to fully explore this chemistry. The rest of this chapter will describe our method for the construction of stereodefined quaternary carbon centres through allylboration chemistry, in addition to reviewing the pioneering work in the field.

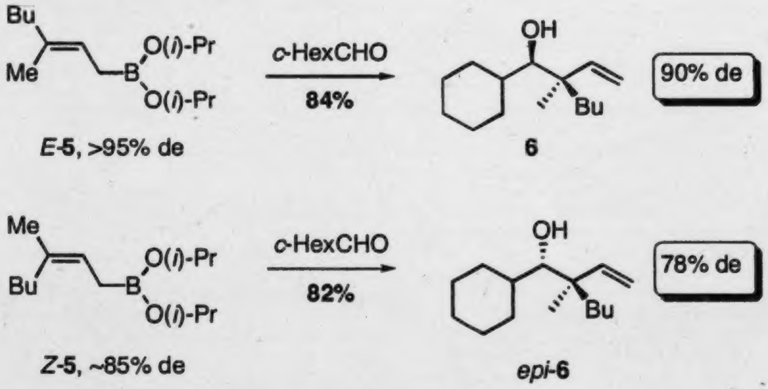
3.1.1 Quaternary carbon centres through diastereoselective allylborations

Hoffmann and Schlapbach were among the first to show that γ-disubstituted allylboronates could be used to generate stereodefined quaternary carbon centres (Scheme 3-1).[3] Although these boronates reacted with aldehydes in the expected manner, the reactions were notably slower than typical allylborations, requiring 5-8 days at room temperature to reach completion. The authors also noted that the diastereomeric purity of the products **4** were lower than the purity of the initial allylboronates **3**. They speculated that this erosion was due to allylation via a competing transition state, in which the aldehyde proton is in the equatorial position rather than the usual axial position to relieve the gauche interaction between the aldehyde R group and the boronate Z-substituent (Figure 3-1, page 46).



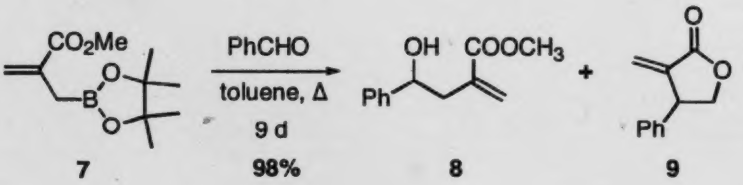
Scheme 3-1

Similar results were reported by Sato and co-workers, except with the isopropyl boronic esters **5** instead of the pinacol esters **3** (Scheme 3-2).[4] Interestingly, these allylboronates also showed small amounts of stereochemical leakage. However, the reaction times were considerably shorter with these reagents than with the pinacol boronates **3** used by Hoffmann and Schlapbach (overnight instead of several days). These shorter reaction times are due to the fact that acyclic boronic esters tend to react faster than analogous, more sterically demanding, cyclic boronic esters.[5]



Scheme 3-2

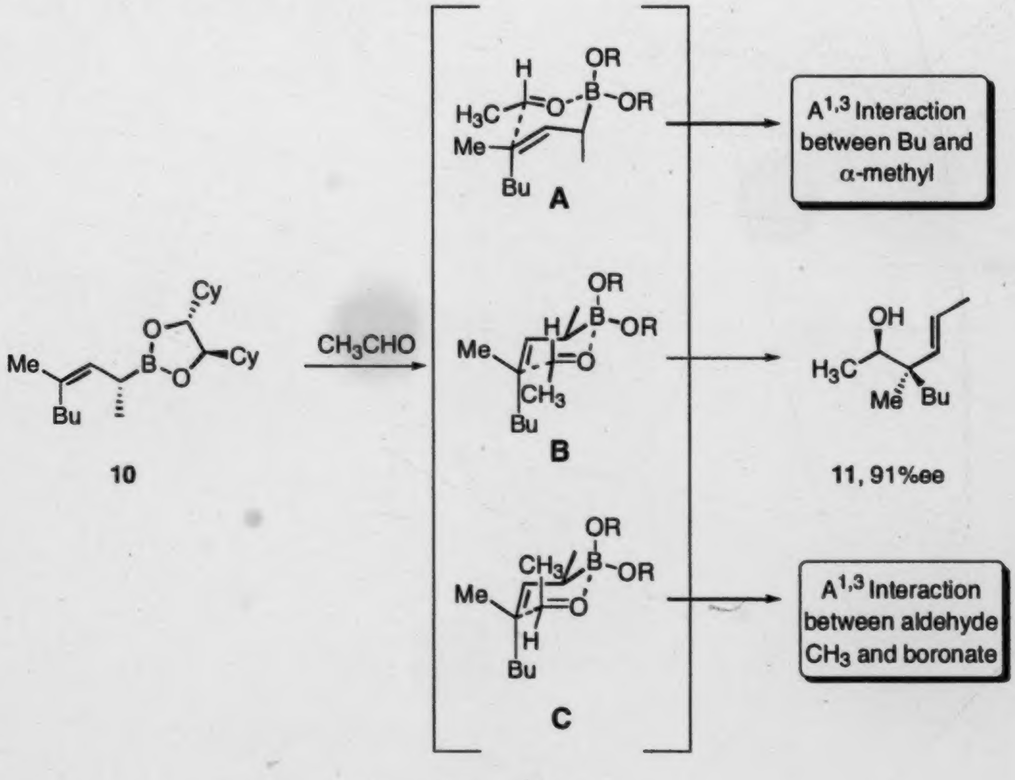
2-Carboalkoxyallylboronates **7** were prepared by Villiéras and co-workers in good yield via the hydroalumination of propiolate esters.[6] Although these reagents are unsubstituted at the γ-position, the study of their allylation reactions yielded several results pertinent to our research (Scheme 3-3). First and foremost, allylations with these ester-substituted reagents **7** were even slower than with Hoffmann and Schlapbach's reagents **3**, and reactions took one to two weeks at room temperature or in refluxing toluene. Another point of interest is that sometimes variable amounts of the butyrolactone **8** are produced along with the expected homoallylic alcohol **9**, especially in refluxing toluene. Indeed, these exo-methylene butyrolactones **9** were the true focus of the Villiéras group's research because they form an important class of biologically active compounds (see Section 3.2.3 below).



Scheme 3-3

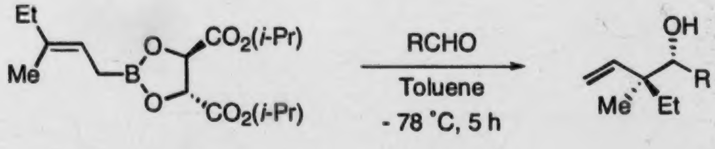
3.1.2 Quaternary carbon centres through enantioselective allylborations

Very few studies have been carried out on enantioselective allylborations with γ-disubstituted allylboronates. An interesting approach to this problem was explored by Hoffmann and co-workers, who used the stereodefined α-substituted allylboronate **10** to induce stereoselectivity (Scheme 3-4).[7] Analysis of the three major transition states suggested that Transition State **B** should be favoured over the other two. This concept was validated in the case of crotylboronates, and the authors showed that the stereoselectivity observed in the additions derived entirely from the stereogenic α-methyl group and not from the 1,2-dicyclohexylethanediol (DICHED) auxiliary.[8] However, allylations with **10** proceeded with very high but not total stereoselectivity. The authors suggest that this lower than expected selectivity might be due to the fact that the allylboronate **10** may not have been prepared stereochemically pure, noting that the diastereomeric purity of **10** could not be assessed before the allylboration reaction.


Cy
O
B
O
Cy
Me
Bu
10
CH$_3$CHO
OR
H
H$_3$C
O
B
OR
Me
Bu
A
A^{1,3} Interaction between Bu and α-methyl
OR
H
B
OR
Me
O
CH$_3$
Bu
B
OH
H$_3$C
Me
Bu
11, 91%ee
OR
CH$_3$
B
OR
Me
O
H
Bu
C
A^{1,3} Interaction between aldehyde CH$_3$ and boronate

Scheme 3-4

Following Roush's methodology,[9] Yamamoto and co-workers achieved moderate success with the tartrate-modified γ-disubstituted allylboronates **12** (Table 3-1).[10] As with Hoffmann's examples, the diastereoselectivity of the reaction was not complete, and the authors do not comment if this loss of selectivity is a reflection of the diastereopurity of the allylboronate or if it is due to stereochemical leakage during the reaction.

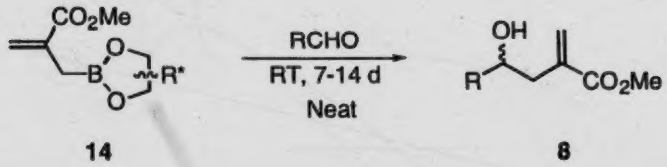


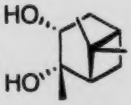
12 **13**

Entry	R	Yield	de (%)	ee (%)
1	C_5H_{12}	75	92	79
2	(i)-Bu	72	92	63
3	$BnO(CH_2)_3$	56	94	73
4	PhCH=CH	100	92	62

Table 3-1. Enantioselective allylborations with tartrate modified γ-disubstituted allylboronates **12**.[10]

Enantioselective allylations with chiral 2-carboxyester allylboronates **14** yielded some interesting results. In contrast to the results shown in Table 3-1, the Villéras group found that most of the usual auxiliaries used for stereoselective reactions with organoboronates (*e.g.*, pinanediol **15**, tartrate esters **16**, Whiting's diol **17**[11]) were not successful with 2-carboxyester allylboronates (Table 3-2).[12] In fact, the only auxiliary that gave useful levels of selectivity was Hoffmann's camphor-derived diol **18**.[13,14]





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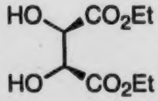
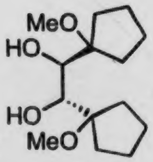


16



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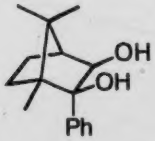


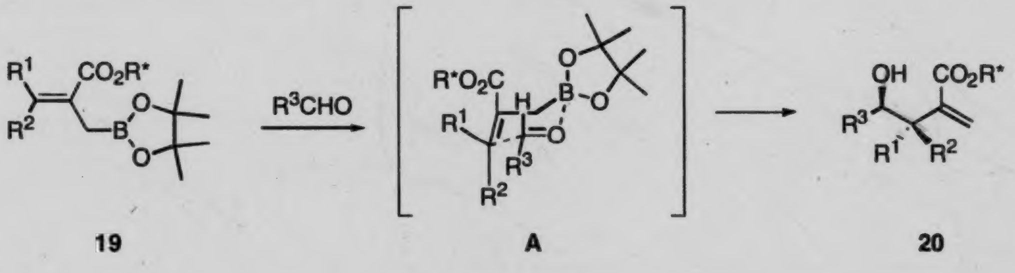
18

Entry	Boronate	R	Diol	Yield (%)	ee (%)
1	**14a**	3,4,5-(MeO)-C_6H_2	**15**	80	6
2	**14b**	4-Cl-C_6H_4	**16**	30	20
3	**14c**	4-Cl-C_6H_4	**17**	90	20
4^a	**14d**	3,4,5-(MeO)-C_6H_2	**18**	88	82

Table 3-2. Enantioselective allylations with chiral 2-carboxyester allylboronates **14**. ^{a} Reaction performed in toluene.[12,13]

3.1.3 Our contribution

Now that we had secured a reliable route to stereodefined tetrasubstituted allylboronates **19** (see Chapter 2), we needed to show that they would indeed react with aldehydes to give homoallylic alcohols **20** containing a quaternary carbon centre. The literature described above gave us ample precedent to suggest that the reaction would proceed with a high level of diastereoselectivity (Scheme 3-5).



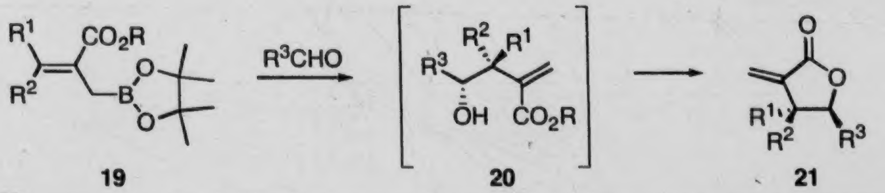
Scheme 3-5

Once we had established suitable conditions for these diastereoselective additions, we intended to investigate enantioselective additions. The first enantioselective allylboration reaction was reported by Hoffmann in 1978,[14,15] and the benchmarks for enantioselectivity have been set by Roush,[9] Brown,[16] and Corey.[17] Unfortunately, we believed that none of these approaches would be effective in the enantioselective generation of quaternary centres using our allylboronates **19**. Brown's chiral allylboranes suffer from facile 1,3-metallotropic rearrangement at temperatures above –78 °C which could lead to scrambling of the geometry of the double bond in boronate **19**. Furthermore, studies from the Villiéras group showed that most boron-based auxiliaries are not effective with 2-carboxyester allylboronates For these reasons, and also because it had not been previously investigated, we decided to explore the use of chiral directing groups on the carboxyester instead of the boronic ester. From the putative transition state **A**, we predicted that an ester-based auxiliary would be necessarily close to the reaction centre and would therefore stand a good chance at controlling the absolute stereochemistry of the addition.

3.2 Stereodefined Quaternary Carbon Centres From Allylboronates 19

3.2.1 Diastereoselective reactions

We were pleased to find that the tetrasubstituted allylboronates **19** underwent a smooth, if somewhat slow, reaction with aldehydes (Table 3-3). In contrast to allylations with unsubstituted 2-carboalkoxyboronates **7**, the product from allylations with **19** was almost always lactone **21,** and the intermediate homoallylic alcohol **20** was only observed in the reaction of monosubstituted boronate **19a** (entry 1). This facile lactonization is likely a manifestation of the *gem*-dialkyl effect.[18]



Entry	Boronate	R^1	R^2	R^3	Lactone	Conditions^a	Yield (%)
1	**19a**	H	Me	Ph	**21a**	B	60
2	**19b**	Me	Me	Ph	**21b**	C	78
3	**19b**	Me	Me	TPSO-CH_2CH_2-	**21c**	E	92
4	**19c**	Me	Bu	*p*-NO_2-C_6H_4-	**21d**	D	67
5	**19d**	Me	(*i*)-Bu	*p*-MeO-C_6H_4-	**21e**	C	50
7	**19e**	Et	Me	*n*-C_9H_{19}	**21f**	A	68
8	**19e**	Et	Me	Ph	**21g**	A	60
9	**19e**	Et	Me	*p*-MeO-C_6H_4-	**21h**	C	47
10	**19e**	Et	Me	*p*-NO_2-C_6H_4-	**21i**	B	81
11	**19j**	Me	Allyl	*p*-MeO-C_6H_4-	**21j**	C	48
13	**19k**	Bu	Me	*p*-NO_2-C_6H_4-	**21k**	B	76
14	**19l**	Ph	Me	*p*-NO_2-C_6H_4-	**21l**	B	26
15	**19m**	TPSOCH_2	Me	*p*-NO_2-C_6H_4	**21m**	B	75

Table 3-3. Allylborations with γ-disubstituted allylboronates **19**. All lactones were isolated in >20 : 1 dr. TPS = (*t*)-Butyldiphenylsilyl. ^{a} Conditions. A: toluene, rt, >12 d; B: toluene, 60-80 °C, 16-120 h; C: toluene, 110 °C, 16-24 h; D: CH_2Cl_2, 40 °C, 48 h; E: neat, rt, >12 d.

These reactions are operationally extremely simple – the aldehyde and boronate are stirred together in toluene, dichloromethane, or even neat. Most aldehydes, both aromatic and aliphatic, are effective substrates in the reaction, and so far the only exceptions found are very hindered aldehydes (*e.g.*, cyclohexanecarboxaldehyde, mesitaldehyde) and aldehydes with free amino groups (4-dimethylaminobenzaldehyde). The only downside is that the reactions are quite sluggish. Similar to the results of Villiéras and co-workers, reaction times are on the order of two weeks at room temperature, but, and in contrast to these published results, only 24 h in hot toluene (60-110 °C).

The large rate differences seen between reactions with γ-disubstituted allylboronates (**3** and **5**) and 2-carboxyester boronates (**7** and **19**) suggest that simple steric arguments cannot explain the low reactivity of **19**. This slow reaction is likely due to a reduction of the nucleophilicity of the γ-carbon in boronates **19** by conjugation to the carboxyester (Figure 3-2). In support of this theory, an unusually slow reaction is also observed with γ-alkoxyallylboronates,[19] where the oxygen can similarly reduce the nucleophilicity at this position by inductive effects. However, reaction times with **19** are dramatically reduced under the new catalytic manifold (see Chapter 4).

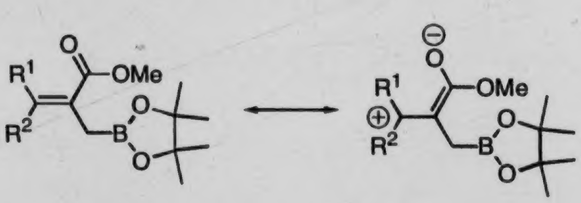
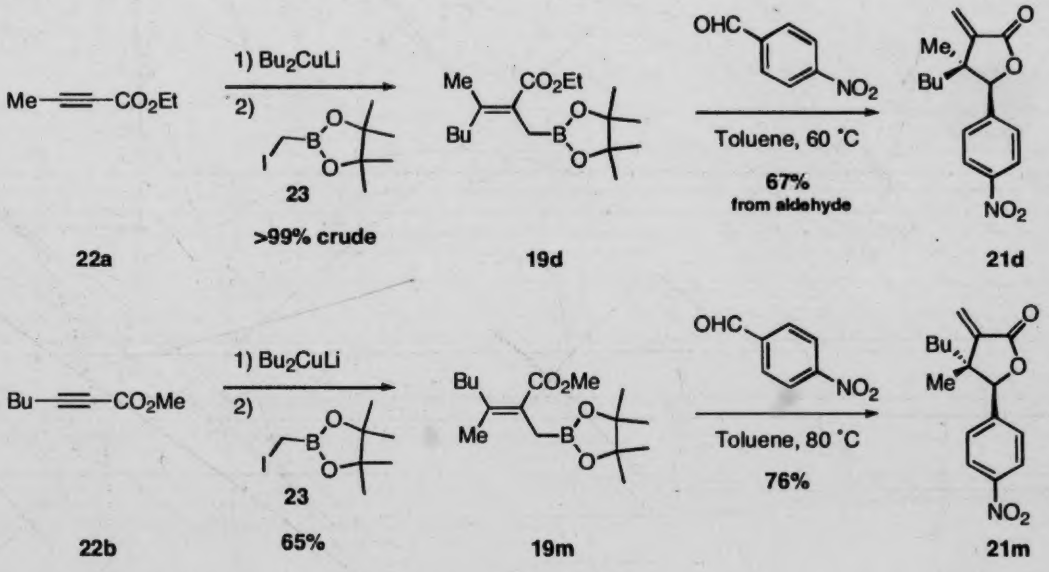


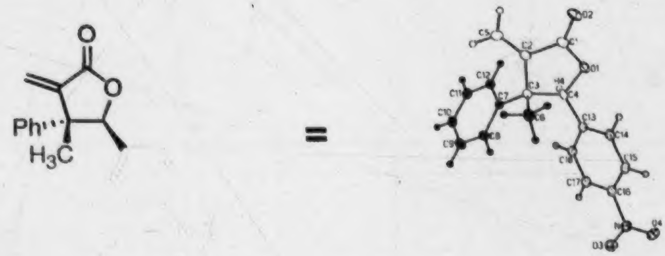
Figure 3-2. Resonance structures for boronate **19**.

Unlike the reactions with the γ-disubstituted boronates **3** and **5**, which lacked the 2-carboxyester group, generally no stereochemical leakage was observed in our reactions. In fact, the reactions are stereospecific – the *Z*-group in boronate **19** (R^2, which derives from the cuprate) is always *syn* in lactone **21** to the group from the aldehyde (R^3). Furthermore, the stereochemical purity of lactone **21** mirrors that of boronate **19**. Thus, if the boronate was a 20:1 mixture of diastereomers, then the lactone is correspondingly a 20:1 diastereomeric mixture. This effect was elegantly demonstrated by the preparation of the epimeric lactones **21d** and **21m** (Scheme 3-6). The only time that these reactions are not stereospecific is when aliphatic aldehydes are reacted at high temperatures. When reactions with these substrates are performed in refluxing toluene, the product lactones do show some erosion of stereoselectivity (see below). This erosion is not observed when the reactions are done at temperatures at or below 80°C, nor are they observed with aromatic substrates at any temperature.

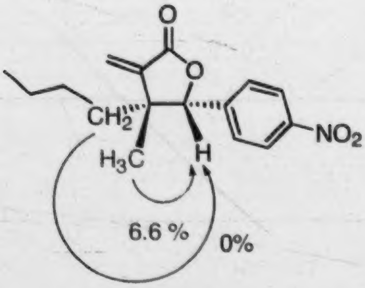


Scheme 3-6

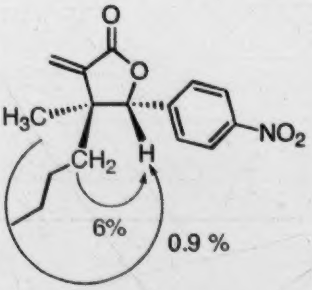
The stereochemistry of the lactone products was determined by ^{1}H nOe experiments on the diastereomeric lactones **21d** and **21m**, as well as by X-ray crystallography of lactone **21n** (Figure 3-3).



21n



21d



21m

Figure 3-3. ORTEP diagram of **21n** and ^{1}H nOe data for lactones **21d** and **21m**.

The diastereomer observed in these reactions is the same as that predicted from simple Zimmerman-Traxler models (Figure 3-4) where the R group from the aldehyde is in the pseudo-equatorial position (Transition State **A**). The stereochemical leakage observed in reactions with **3** and **5** (γ-disubstituted allylboronates which lack this ester group) is not observed here. The reason for this result is likely that in the competing Transition State **B**, the R^3 group and the 2-carboxyester group would experience an unfavourable 1,3-diaxial interaction in addition to the usual 1,3-interaction between the R^3 group and the axial boronate substituent. The additional steric interaction effectively prevents Transition State **B** from competing with Transition State **A**.

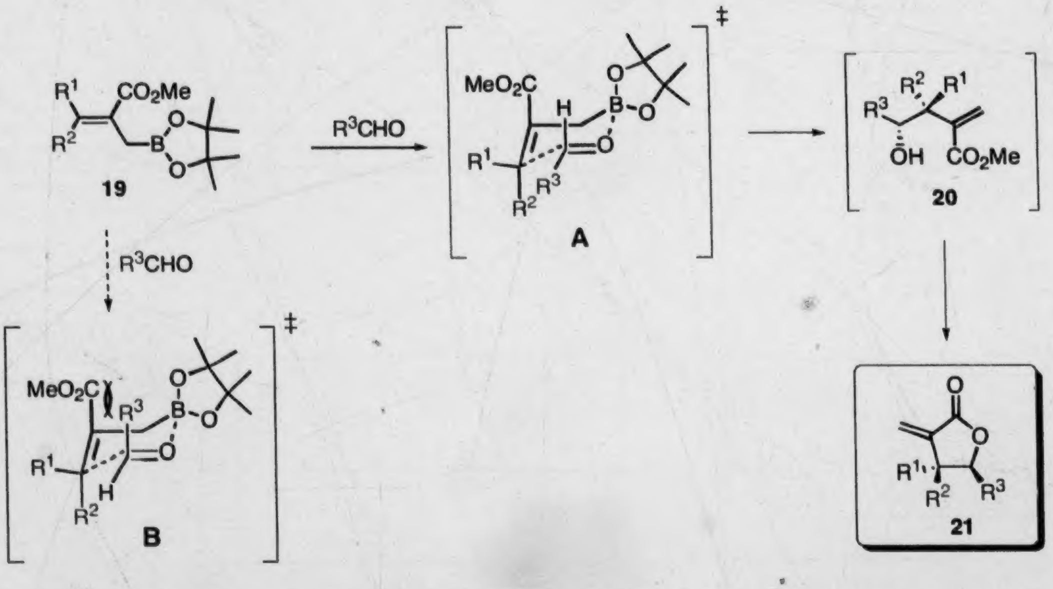
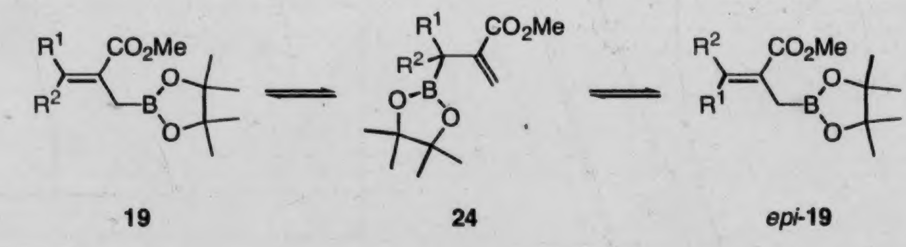


Figure 3-4. Proposed mechanistic pathway for allylborations with α-alkoxycarbonyl allylboronates **19**.

Finally, there remains to explain the erosion of stereochemical purity observed in the reactions of aliphatic aldehydes in refluxing toluene. One possible explanation is that the boronate undergoes reversible borotropic rearrangement at these temperatures (Scheme 3-7),[1] thus leading to "isomerized" products after the allylboration. However, if that were the case, then aromatic aldehydes should also show some levels of erosion. Furthermore, recovered boronate from these reactions does not show evidence of isomerization. Another, more likely possibility is that other transition states are becoming energetically attainable at these higher temperatures. This explanation was the one offered by Hoffmann and Schlapbach to explain the erosion of stereochemistry seen with the γ-disubstituted allylboronates **3**.[3] While Transition State **B** in Figure 3-4 is the most likely candidate, we cannot exclude the possibility that boat-like transition states which lead to the other diastereomer may also be operative.



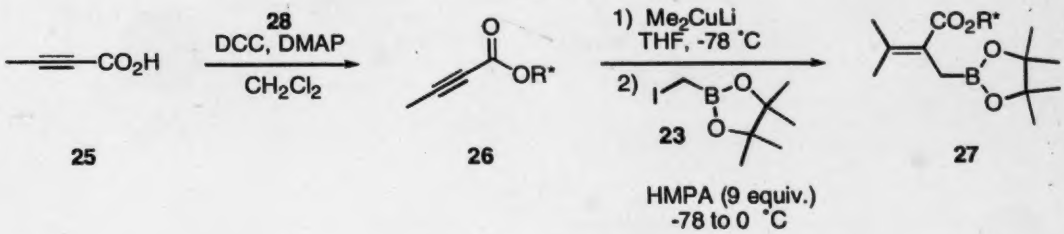
Scheme 3-7

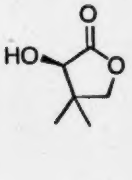
3.2.2 Enantioselective reactions

The next step in the project was to extend the methodology to enantioselective additions. Inspection of the structure of boronate **19** reveals that there are two positions where a chiral auxiliary could be installed – either on the carboxyester or on the boronate. Since the Villiéras group had extensively studied the effect of known boron based chiral diol directors and found that most were ineffective with 2-carboxyester allylboronates **14** (see Section 3.1.2), we decided to explore the effectiveness of a carboxyester based auxiliary.

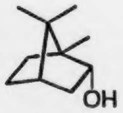
3.2.2.1 Single auxiliary approach

Chiral 2-carboxyester allylboronates **27** were prepared by the DCC mediated esterification[20] of 2-butynoic acid **25** with various chiral alcohols **28**[21] followed by carbocupration and trapping with **23** as described in Chapter 2 (Table 3-4). Since we initially doubted the stability of the boronates **27**, they were generally used crude in the subsequent reactions. However, we later found that these boronates could be readily purified by silica gel chromatography.

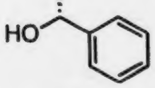




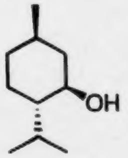
28a



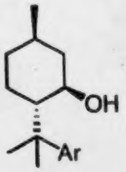
28b



28c



28d

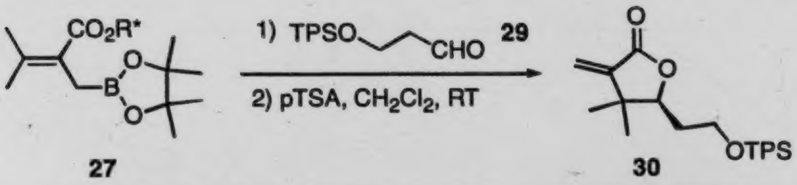


28e: Ar = Phenyl
28f: Ar = 2-Naphthyl
28g: Ar =4-$MeOC_6H_4$
28h: Ar = 4-PhC_6H_4
28i: Ar = 3,5-$Me_2C_6H_3$

Entry	Chiral Alcohol	Alkynoate	Yield of **26** (%)	Boronate	Crude Yield of **27** (%)
1	**28a**	**26a**	89	**27a**	>99
2	**28b**	**26b**	80	**27b**	>99
3	**28c**	**26c**	79	**27c**	98
4	**28d**	**26d**	78	**27d**	94
5	**28e**	**26e**	89	**27e**	44[a]
6	**28f**	**26f**	82	**27f**	>99
7	**28g**	**26g**	65	**27g**	>99
8	**28h**	**26h**	35	**27h**	>99
9	**28i**	**26i**	43	**27i**	>99

Table 3-4. Preparation of chiral alkynoates **26** and boronates **27**. [a] Product purified by silica gel chromatography.

We chose aldehyde **29** as an aliphatic, non-volatile, model substrate.[22] Subsequent allylations of aldehyde **29** with chiral boronates **27** were performed at room temperature over 10-14 days and the enantiopurity of the lactone products **30** was determined by chiral HPLC (Table 3-5). In reactions with the very large arylmenthol auxiliaries (entries 5-9), lactonization of the homoallylic alcohol was not spontaneous. In these cases, the cyclization was promoted by treatment of the crude reaction mixture with mild acid.



Entry	Boronate	Conditions	Lactone	Yield	ee (%)
1	**27a**	Neat, 8 d	**30a**	89	22
2	**27b**	Neat, 14 d	**30b**	64	(- 6)[a]
3	**27c**	Toluene, 26 d	**30c**	70	10
4	**27d**	Neat, 8 d	**30d**	78	7
5	**27e**	Toluene, 36 d	**30e**	51	80
6	**27f**	Toluene, 14 d	**30f**	(95)[b]	82
7	**27f**	CH_2Cl_2, 14 d	**30f**	(86)[b]	75
8	**27g**	Toluene, 14 d	**30g**	74	56
9	**27h**	Toluene, 14 d	**30h**	24	66
10	**27i**	Toluene, 14 d	**30i**	6	62

Table 3-5 Enantioselective allylations with boronates **30a-i**. Yields calculated after silica gel chromatography. Selectivities were determined by Chiral HPLC. See Experimental Section for details. The absolute configuration is inferred from other results, see below for details. TPS = (*t*)-Butyldiphenylsilyl. [a] Major isomer is opposite to that in the other entries. [b] Product contaminated with auxiliary. While this contamination gives an artificially high yield, it did not affect the HPLC analysis.

Gratifyingly, we found that a carboxyester based chiral auxiliary could effectively direct the stereochemical course of the reaction (Table 3-5). Simple chiral alcohols **28a-d** were not effective in this reaction (entries 1-4), but the leap in selectivity observed with the 8-arylmenthol auxiliaries **28e-i** is remarkable (entries 5-10). This increase is especially impressive given the poor performance of menthol **28d** (the parent compound, entry 4). We also noticed a small solvent effect, where selectivities were higher when the reaction was performed in toluene rather than in dichloromethane (compare entries 6 and 7).

We were encouraged by the effectiveness of the 8-phenymenthol ester **27e** in the reaction (entry 5), and it seemed only a matter of modifying the aromatic ring to find the auxiliary that would provide truly effective levels of stereoinduction. Unfortunately, enantioselectivities greater than 82% were not achieved, despite the use of a large number of different arylmenthols, and there currently seems to be no advantage to using auxiliaries other than the commercially available phenyl derivative **28e**.

The power of 8-arylmenthol esters in stereoselective cyclizations,[21,23] Michael additions[24] and allylsilations[25] is well documented, and their effectiveness is generally attributed to the ability of the aromatic ring to shield one face of the reacting olefin.[26] In the case of these allylborations, the phenyl ring presumably shields one of the faces of the allyl group. Indeed, an X-ray crystal structure of **27f** shows that the β-naphthyl group effectively covers the *Re*-face of the allylboronate (as determined from C2, Figure 3-5). Similarly, ^{1}H NMR spectroscopy of **27f** shows that the signals for the protons on C4, C5 and C6 are all shifted significantly upfield compared to the analogous methyl ester **19b**, an effect that would be expected from diamagnetic shielding from the naphthyl ring. Similar shielding effects are observed in the other α,β-unsaturated arylmenthol esters.[26]

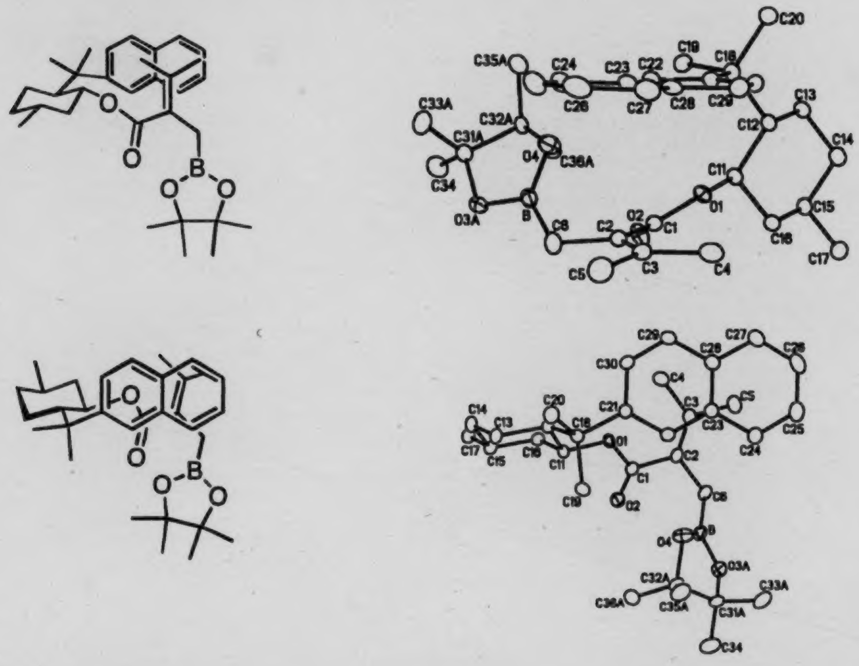


Figure 3-5. ORTEP diagrams of boronate **27f**, two different views, with Chemdraw structures for reference.

In analogy to the results from the enantioselective additions with the dual auxiliary boronate **31a** (see next section), the (*S*)-configuration has been assigned to the major enantiomer of lactone **30** produced in these reactions. From HPLC data, all of the auxiliaries studied to date give the same major enantiomer of the lactone **30**. The only exception is entry 2, where the borneol **27b** derived boronate favoured the opposite enantiomer of the lactone **30**. However, it might be argued whether a 6% ee points to a significant preference for one enantiomer over the other or if it suggests that the auxiliary really had no overall effect on the reaction.

At this point in the study it would be premature to propose a transition state to explain this stereoselectivity, even with the crystal structure in Figure 3-5. A simple, Zimmerman-Traxler model with preferential *Si*-face attack of the aldehyde would predict that (*R*)-**30** should be the preferred isomer. There are several reasons why this simple model fails to accurately predict the stereochemical outcome of the allylation. Firstly, the transition state of the reaction may not resemble the solid state structure of boronate **27f**, although it is encouraging to see that the aromatic ring still effectively shields the olefin in the solution state. A larger concern is that the reactive conformer of the boronate in the transition state may not be the same as its solid state structure. For example, both conformers of **27f** in Figure 3-6 would show the observed diamagnetic shielding of the allylic protons in the ^{1}H NMR, even though they expose different faces of the olefin. Also, we cannot be certain that the aldehyde would prefer to approach the *Si*-face of the boronate due to a shielding effect of the aromatic ring, or if it would prefer to approach the *Re*-face of the olefin by a directing effect of the ring. Although this latter approach would require the aldehyde to squeeze in between the aromatic ring and the boronate and thus might seem unlikely, a similar mode of action has been proposed for the selective reactions with Hoffmann's bornanediol modified boronates (see next section).[14]

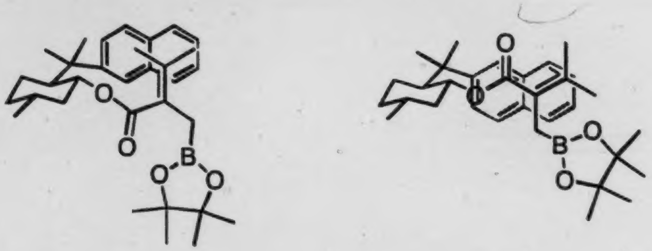


Figure 3-6. Possible conformations for boronate **27f**.

3.2.2.2 *Dual auxiliary approach*

Since we were unable to achieve sufficiently high levels of enantioselectivity with a single chiral auxiliary, we decided to explore a dual auxiliary approach (Figure 3-7). We envisaged that boronate **31a**, which bears a chiral auxiliary on both the carboxyester and boronic ester would provide high levels of selectivity. We chose to focus on Corey's 8-phenylmenthol **28e** and Hoffmann's bornanediol-derived **18** since these two auxiliaries were previously shown to be the most effective auxiliaries for 2-carboxyester allylboronates (see above).

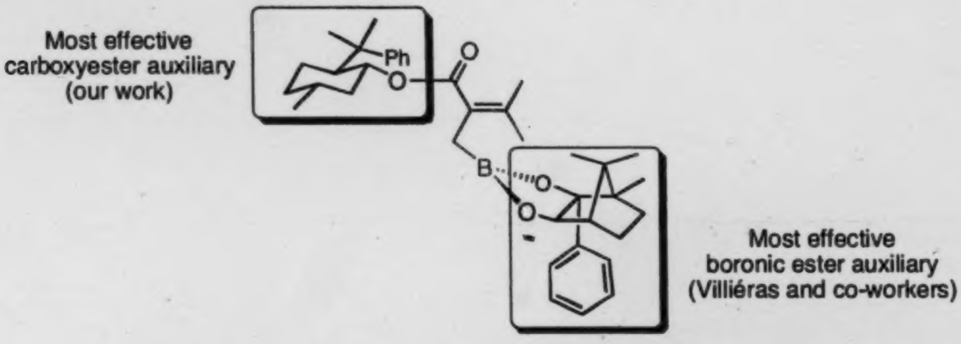
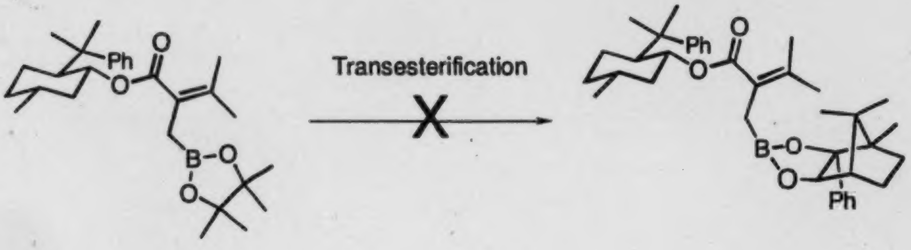


Figure 3-7. Design of the dual-auxiliary α-alkoxycarbonylboronate **31a**.

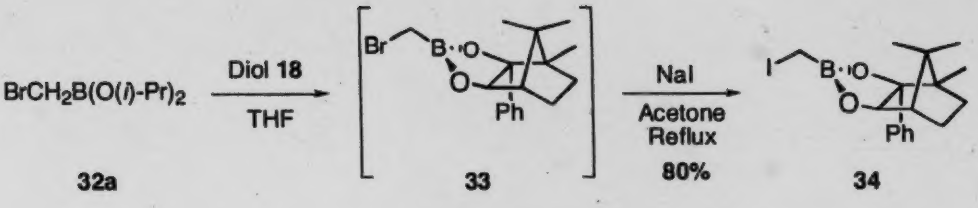
We attempted several preparations of boronate **31a** before finally finding an effective route. A simple preparation would entail replacement of the pinacol in boronate **27e** for diol **18** (Scheme 3-8). However, despite literature precedents for this transformation,[12a,27] all attempts to transesterify the pinacol ester **27e** failed in our hands.



27e **31a**

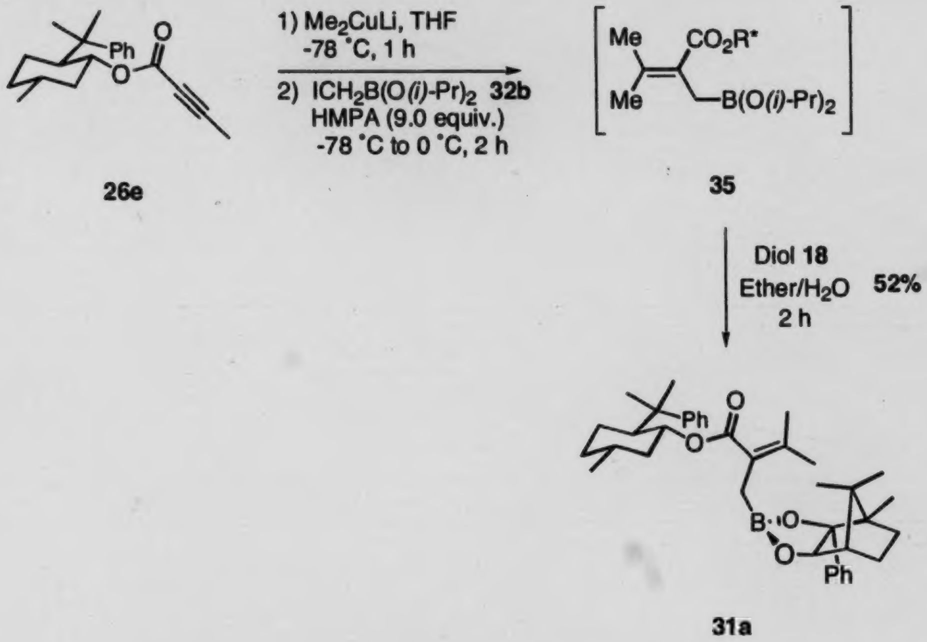
Scheme 3-8

We next prepared chiral electrophile **34** by transesterification of the diisopropyl bromomethaneboronate **32a**[28] followed by halogen exchange on the intermediate bromide **33** (Scheme 3-9),[29] hoping to use it in place of the pinacol electrophile **23** in the carbocupration-alkylation sequence described in Chapter 2. Unfortunately, although we were able to prepare **34**, it did not give an effective electrophilic quench in the subsequent carbocupration reaction.



Scheme 3-9

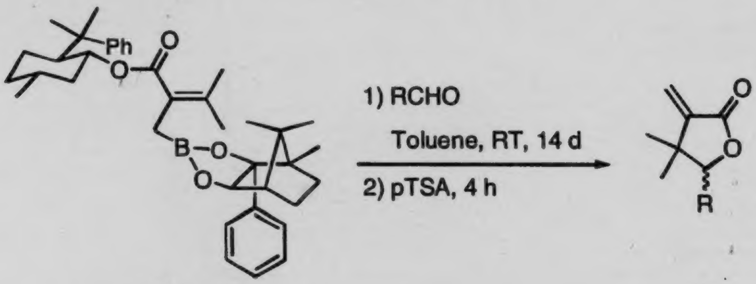
We were finally able to access boronate **31a** by transesterification of the diisopropyl allylboronate **35** (Scheme 3-10).[30] The boronate **35** was not isolated but rather treated with an ethereal solution of **18** in the workup, directly yielding the desired boronate **31a**.



Scheme 3-10

We were delighted to see that this dual auxiliary strategy did indeed afford a highly enantioselective allylating reagent. Stirring boronate **31a** in toluene with aldehydes for two weeks at room temperature followed by acid-catalysed ring closure gave acceptable yields of enantioenriched lactones **36** (Table 3-6). Both an aliphatic and an aromatic aldehyde were effective in this reaction. Although the requirement for two different auxiliaries might appear excessive, the enantioselectivities obtained are excellent. Furthermore, the methodology is partially redeemed by the facile removal of the auxiliaries from the product.

Both auxiliaries are simultaneously removed in the final cyclization, alleviating the need for separate cleavage steps. Even though the ^{1}H NMR spectrum of the crude mixture suggests that both auxiliaries are present and therefore potentially recoverable, the small scale at which these reactions were run made this recovery impractical.

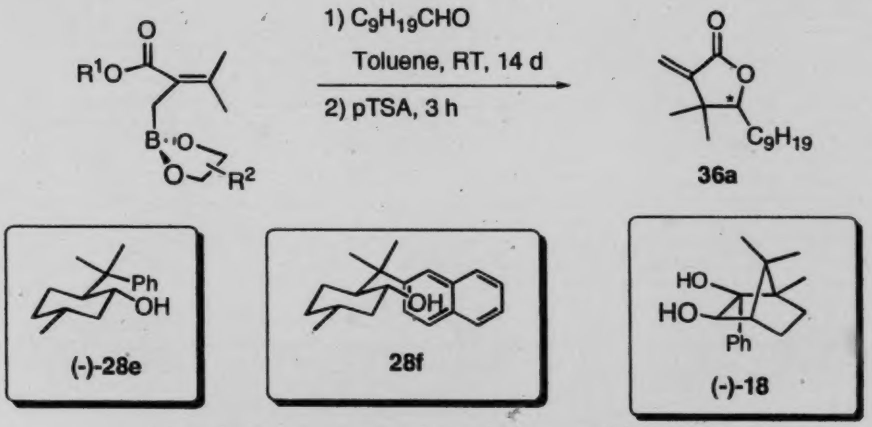


31a **36**

Entry	Lactone	R	Yield (%)	ee (%)
1	**36a**	C_9H_{19}	80	97
2	**36b**	Ph	55	>95 [a]
3	**36c**	*p*-Br-C_6H_4-	40	>95 [a]

Table 3-6. Enantioselective additions with boronate **31a**. Enantioselectivities determined by Chiral HPLC. See Experimental section for details. [a] Selectivity uncertain because of poor baseline resolution of the enantiomers. 95% is the lowest, most conservative estimate.

We next determined that these high selectivities were a result of a matched combination of the (-)-8-phenylmenthol **28e** and the (-)-isomer of bornanediol **18**. As seen in Table 3-7, the selectivities observed with these two auxiliaries are higher than selectivities observed with only one or the other, and are much higher than the mismatched combination of (-)-8-phenylmenthol **28e** and the (+)-isomer of bornanediol **18**. It should be noted that the result in entry 4 is from the β-naphthyl boronate **27f** and not from the parent 8-phenylmenthol **27e**. Nevertheless, **27f** is an appropriate control substrate for this study since these two boronates gave comparable results in the single auxiliary study (see preceding section).



Entry	Boronate	R¹	Diol	ee (%)
1	**31a**	(-)-**28e**	(-)-**18**	97
2	**31b**	(-)-**28e**	(+)-**18**	<10
3	**37**	Ethyl	(-)-**18**	50
4	**27f**	**28f**	Pinacol	82

Table 3-7. Matched and mis-matched auxiliary studies on boronate **31**.

We were able to establish that lactone **36c** has the (*S*)-configuration by X-ray crystallography (Figure 3-8), and all other assignments were made in analogy to this result.

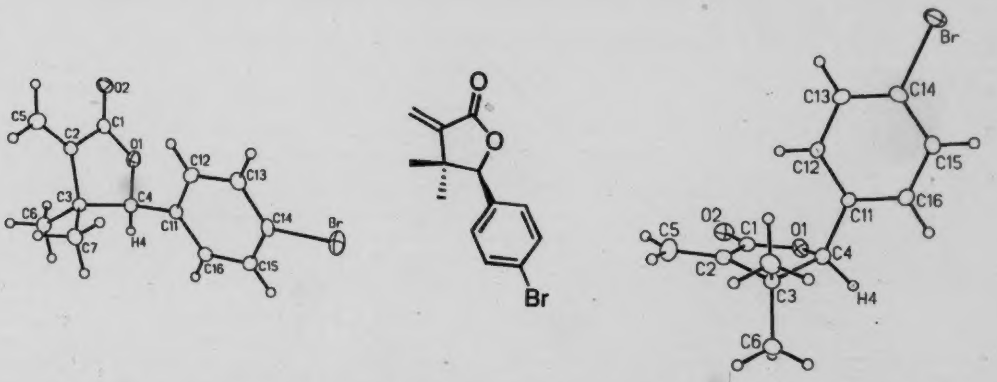


Figure 3-8. ORTEP diagrams of enantiopure lactone **36c**, with a Chemdraw structure for reference.

We are not in a position were we can offer a transition state model which incorporates both the phenylmenthol auxiliary **28e** as well as the bornanediol **18** in the stereodifferentiating step. However, the simple model proposed by Villiéras and co-workers to explain the stereochemical outcome of reactions with boronates featuring only **18** accurately predicts that the (*S*)-isomer should be produced in these reactions (Figure 3-9).[13,14]

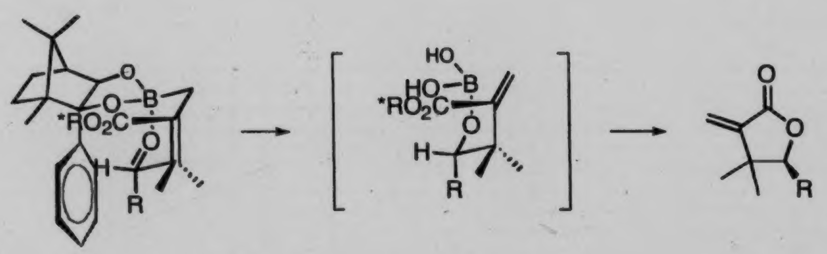


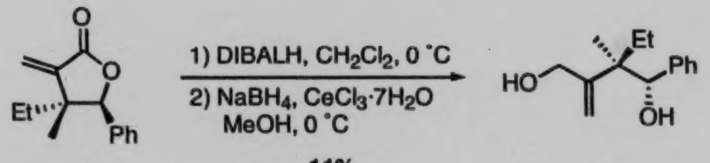
Figure 3-9. Model for stereoinduction proposed by Villiéras and co-workers.[13]

3.2.3 Further functionalization of lactones 21

The products of the allylboration reactions described thus far are exo-methylene butyrolactones **21**. These compounds form a family of biologically active natural products, which have shown promise as potential therapeutics in the treatment of cancer,[31] infection and alcoholism.[32] The biological activity of these compounds is proposed to derive primarily from their ability to act as Michael acceptors for suitable nucleophiles (*e.g.*, the thiol of a cysteine residue).[32,33] However, most of these compounds are quite toxic, and the need for analogues has spurred interest in establishing synthetic routes to these butyrolactones.[34,35]

Notwithstanding the inherent value of this class of compounds, the focus of our research was truly the generation of stereodefined quaternary carbon centres rather than the establishment of a new route to these butyrolactones. We believed that our methodology would find wider application and use if the resulting quaternary carbon centres were not necessarily confined to a five-membered ring. To this end, both the ester functionality and the exocyclic olefin provide useful handles for the further transformation of the lactones into other structures. This section will describe our preliminary efforts in this direction.

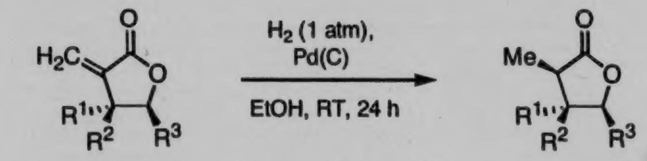
One of our primary goals was the reductive opening of the lactone **21** to the corresponding acyclic diol **38** (Scheme 3-11). The product of this reduction would be a very versatile synthetic intermediate, a diol which possesses easily differentiated primary and secondary alcohols as well as an allylic alcohol. To achieve this reduction, a two step procedure reported by Matsuda and co-workers looked promising.[36] Although the reduction proceeded to give the diol without concomitant reduction of the olefin, the low yield suggests that the regioselectivity in the reduction is not complete.


1) DIBALH, CH_2Cl_2, 0 °C
2) $NaBH_4$, $CeCl_3 \cdot 7H_2O$
MeOH, 0 °C
O
O
Et
Ph
HO
Et
Ph
OH

21a 11% **38**

Scheme 3-11

We also investigated simple hydrogenation of the exocyclic double bond in **21**. Although the product of this reduction is still a cyclic structure, it contains three contiguous stereogenic centres, and we expected that the cyclic nature of the substrate might help control the stereochemistry of the hydrogenation. In the event, this reduction exceeded our expectations, and the olefin underwent a highly selective reduction under mild conditions to give only one diastereomer of the α-methyl lactone **39** (Table 3-8). No other isomer of the product could be detected by ^{1}H NMR spectroscopy. Pleasingly, no benzylic C-O cleavage was observed with the aromatic lactones under these conditions (entries 3 and 4).



21 **39**

Entry	Lactone	Product	R^1	R^2	R^3	Yield (%)
1	**21p**	**39a**	Et	Me	$PhCH_2CH_2$-	88
2	**21g**	**39b**	Et	Me	C_9H_{19}	85
3	**21a**	**39c**	Et	Me	Ph	86
4	**21e**	**39d**	Me	(*i*)-Bu	4-$MeOC_6H_4$-	81

Table 3-8. Diastereoselective hydrogenation of lactones **21**. The preparation of lactone **21p** is described in Chapter 4.

The stereochemistry of the lactone **39d** was determined by X-ray crystallography, showing that the hydrogen had added from the face opposite to the R^3 group (Figure 3-10). The stereochemistry of the other products was then inferred from this result.

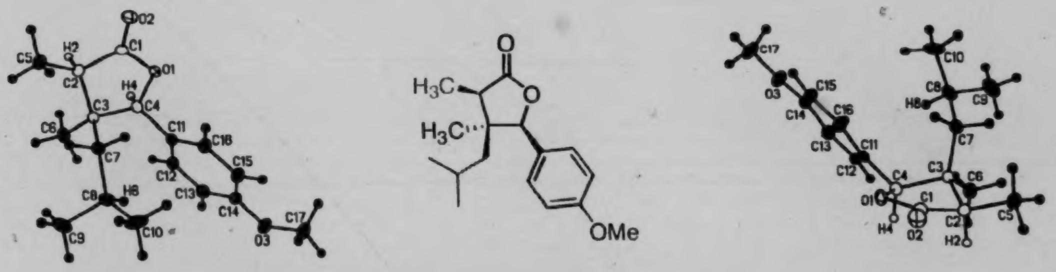
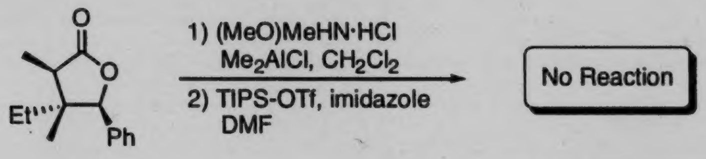


Figure 3-10. Two ORTEP diagrams for the X-ray crystal structure of α-methyl lactone **39d**. A Chemdraw structure is included for reference.

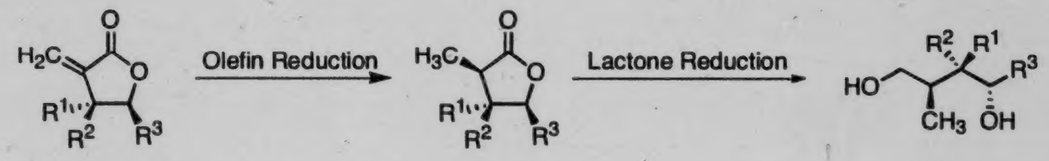
We next attempted to open the reduced lactone **39c** through conversion to the Weinreb amide.[37] However, all efforts to effect this transformation inevitably gave unchanged starting material or complex mixtures (Scheme 3-12). We suspect that even if the reaction does proceed then lactonization of the resulting amide is so favourable that the ring simply snaps shut again.



39c

Scheme 3-12

Our long term goal was to combine the two reductive procedures to produce acyclic stereochemical triads **40** (Scheme 3-13), a structural motif found in many natural products. The generation of multiple contiguous stereogenic centres is still a challenge in synthetic chemistry, especially when one of these centres is quaternary.[38] Efforts towards establishing an efficient, succinct and general route to these structures are in progress in the Hall labs.



21 **39** **40**

Scheme 3-13

3.3 Experimental

The methods described in Section 2.3.1 (page 34) also apply here, with the following additions. All aldehydes were purified by Kugelrohr distillation prior to use. 8-Arylmenthols **28f-h** were made according to published procedures;[21] arylmenthol **28i** was prepared in analogy to these procedures. Bornanediol **18** was prepared by Naheed Rajabali according to a literature procedure.[14] 3-(*tert*-Butyldiphenylsilyloxy)propanal,[22] diisopropyl bromomethaneboronate **32a**[28] and diisopropyl iodomethaneboronate **32b**[30] were prepared via literature procedures. (*R*)-Pantolactone **28a**, *l*-borneol **28b**, (*R*)-1-phenylethanol **28c**, (-)-menthol **28d**, and (-)-8-phenylmenthol **28e** were purchased from commercial sources and used as received. The preparation of lactone **21p** will be described in Chapter 4. Chiral HPLC analysis was performed using a CHIRALPAK AD-RH column (0.46 cm x 15 cm) or a CHIRALCEL OD column (0.46 cm x 25 cm) with UV detection at 210 nm.

3.3.1 Lactones 21 from diastereoselective allylborations with 19

3.3.1.1 *(4R*, 5S*)-4-Methyl-3-methylidene-5-pheny-dihydro-furan-2-one 21a*

A solution of boronate **19a** (298 mg, 1.24 mmol) and benzaldehyde (66 mg, 0.63 mmol) in toluene (2 mL) were heated at 80 °C for 64 h. The mixture was then washed with $NH_4Cl_{(aq)}$ (10 mL) and extracted with Et_2O (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (25% Et_2O/Hexanes, 10 g silica) to give a mixture of the lactone and the γ-hydroxyester. This mixture was stirred overnight in CH_2Cl_2 (5 mL) with a spatula tip of pTSA. The reaction was then quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with ether (3 x 5 mL). The combined ether layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the desired lactone (70 mg, 0.37 mmol, 60%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 3H), 7.18 (m, 2H), 6.33 (d, J = 2.8 Hz, 1H), 5.59 (d, J = 8.1 Hz, 1H), 5.55 (d, J = 2.6 Hz, 1H), 3.42 (m, 1H), 0.77 (d, J = 7.0 Hz, 3H).

3.3.1.2 *rac-4,4-Dimethyl-3-methylene-5-phenyl-dihydro-furan-2-one 21b*

Boronate **19b** (237 mg, 0.885 mmol) and benzaldehyde (62 mg, 0.58 mmol) in CH_2Cl_2 (1 mL) were refluxed under Ar. After 60 h the reaction was concentrated to give the crude products. Flash chromatography (13 g silica, 25-50% CH_2Cl_2/Hexanes) gave the product as a white solid (92 mg, 0.45 mmol, 78%). The compound could be further purified by Kugelrohr distillation (0.1 torr, 225 °C) to give an analytically pure sample (83 mg, 0.41 mmol, 71%).

mp = 48 - 50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 3H), 7.22 (m, 2H), 6.24 (s, 1H), 5.50 (s, 1H), 5.14 (s, 1H), 1.37 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 145.5, 135.7, 128.4, 128.3, 125.9, 120.1, 88.1, 43.6, 25.9, 24.3; IR (CH_2Cl_2 cast, cm^{-1}): 3070, 2977, 1763, 1658, 1124, 751, 707; HRMS (EI, *m/z*) Calcd for $C_{13}H_{14}O_2$: 202.09938. Found: 202.09926; Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.19; H, 6.99. Found: C, 76.94; H, 7.08.

3.3.1.3 rac-5-(2-(tert-butyldiphenylsilyloxy)ethyl)-4,4-dimethyl-3-methylene-dihydro-furan-2-one 21c

3-(*tert*-Butyldiphenylsilyloxy)propanal **29** (308 mg, 1.15 mmol) and boronate **19b** (289 mg, 0.924 mmol) were stirred neat at RT for 12 d. The crude mixture was then purified directly by flash chromatography (22 g silica, 5% EtOAc/Toluene) to give the product as a colourless oil (340 mg, 0.832 mmol, 90%). Kugelrohr distillation (0.1 torr, 225 °C) afforded an analytical sample (282 mg, 0.690 mmol, 75%).

TLC (5% EtOAc/Toluene, $KMnO_4$): 0.40; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.40 (m, 6H), 6.14 (s, 1H), 5.46 (m, 1H), 4.30 (dd, J = 10.4 Hz, 2.6 Hz, 1H), 3.84 (m, 2H), 1.72 (m, 2H), 1.21 (s, 3H), 1.04 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 146.1, 135.4, 133.5, 129.7, 127.7, 119.1, 83.3, 60.2, 41.5, 32.8, 26.8, 24.9, 22.8, 19.1; IR (CH_2Cl_2 cast, cm^{-1}): 3070, 2960, 1767, 1650, 1600, 1296, 1194, 1112, 740, 702; HRMS (EI, *m/z*) Calcd for $C_{21}H_{23}O_3Si$: 351.14166. Found: 351.14269; Anal. Calcd for $C_{21}H_{23}O_3Si$: C, 73.47; H, 7.91. Found: C, 73.00; H, 7.96.

3.3.1.4 (4R, 5R*)-4-Butyl-4-methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one 21d*

Boronate **19c** (222 mg, 0.717 mmol) and *p*-nitrobenzaldehyde (79 mg, 0.52 mmol) in CH_2Cl_2 (1 mL) were refluxed under Ar. After 48 h the reaction was concentrated to give the crude product. Flash chromatography (19 g silica, 5% EtOAc/Toluene) gave a mixture of 3 compounds. Further chromatography (10 g silica, 25% Et_2O/Hexanes) gave the product as a colourless oil (104 mg, 0.360 mmol, 69%). Kugelrohr distillation (0.1 torr, 225 °C) gave an analytically pure sample (101 mg, 0.349 mmol, 67%).

TLC (50% Et_2O/Hexanes, UV/$KMnO_4$): 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (AB, J = 8.6 Hz, 2H), 7.34 (AB, J = 8.4 Hz, 2H), 6.38 (s, 1H), 5.50 (s, 1H), 5.36 (s, 1H), 1.67 (m, 2H), 1.36 (m, 2H), 0.94 (m, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 147.9, 144.2, 142.2, 126.9, 123.7, 122.5, 84.9, 46.8, 40.6, 26.2, 23.2, 23.0, 13.9; IR (CH_2Cl_2 cast, cm^{-1}): 3083, 2952, 1771, 1659, 1607, 1522, 1349, 1105; HRMS (EI, *m/z*) Calcd for $C_{11}H_{18}O_2$: 182.13068. Found: 182.13093; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 77.73; H, 7.47. Found: C, 78.07; H, 7.77.

3.3.1.5 (4R*, 5R*)-5-(4-Methoxyphenyl)-4-methyl-3-methylene-4-(2-methylpropyl)- dihydrofuran-2-one 21e

A solution of boronate **19d** (280 mg, 0.902 mmol) and *p*-anisaldehyde (111 mg, 0.813 mmol) in toluene (1 mL) were heated at 110 °C for 24 h. The solvent was then removed and the residue purified by flash chromatography (25% Et_2O/Hexanes, 20 g silica) to give the title lactone (145 mg, 0.528 mmol, 65%).

TLC (50% CH_2Cl_2/Hexanes, UV/$KMnO_4$): 0.32; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (AB, *J* = 8.9 HZ, 2H), 6.89 (AB, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 0.6 Hz, 1H), 5.51 (d, *J* = 0.5 Hz, 1H), 5.03 (s, 1H), 3.81 (d, *J* = 0.6 Hz, 3H), 1.45 (m, 1H), 1.33 (s, 3H), 1.14 (dd, *J* = 14.4 Hz, 4.6 Hz, 1H), 0.70 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 159.5, 144.4, 127.5, 126.6, 120.5, 113.7, 88.7, 55.3, 47.7, 42.9, 25.4, 25.0, 23.5, 22.3; IR (CH_2Cl_2 cast, cm^{-1}) 2958, 1770, 1659, 1613, 1386, 1366, 1251, 817; HRMS (EI, *m/z*) Calcd for $C_{17}H_{22}O_3$: 274.15689. Found: 274.15618; Calcd for $C_{17}H_{22}O_3$: C, 74.41; H, 8.10. Found: C, 74.06; H, 8.11.

3.3.1.6 (4R*, 5S*)-4-Ethyl –4-methyl-3-methylene-5-nonyl-dihydro-furan-2-one 21f

Decanal (161 mg, 1.03 mmol) and boronate **21e** (435 mg, 1.54 mmol) were stirred at RT under N_2 in toluene (1 mL) for 48 d. The solvent was then evaporated and the crude mixture was purified by flash chromatography (30 g silica, 5% EtOAc/Toluene) to give the product as a colourless oil (225 mg, 0.844 mmol, 82%). The compound was then further purified by Kugelrohr distillation (0.1 torr, 200 °C) to give an analytically pure sample (186 mg, 0.700 mmol, 68%).

TLC (5% EtOAc/Toluene, $KMnO_4$): 0.70; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (s, 1H), 5.39 (m, 1H), 4.16 (dd, *J* = 10.2 Hz, 2.9 Hz, 1H), 1.6-1.2 (m, 18H), 1.08 (s, 3H), 0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 144.1, 120.2, 88.0, 85.6, 45.1, 32.9, 31.9, 31.7, 29.6, 29.56, 29.55, 29.3, 26.2, 22.7, 20.3, 14.2, 8.4; IR (CH_2Cl_2 cast, cm^{-1}): 2924, 1766, 1660, 1109; HRMS (EI, *m/z*) Calcd for $C_{17}H_{30}O_2$: 266.2245. Found: 266.22387; Anal.

Calcd for $C_{17}H_{30}O_2$: C, 76.62; H, 11.37. Found: C, 76.67; H, 11.44.

3.3.1.7 (4R*, 5S*)-4-Ethyl -4-methyl-3-methylene-5-phenyl-dihydro-furan-2-one 21g

Boronate **21e** (413 mg, 1.46 mmol) and benzaldehyde (105 mg, 0.992 mmol) in toluene (1 mL) were stirred at RT under N_2 for 48 d. The mixture was then concentrated and the residue was purified by flash chromatography (30 g silica, 5% EtOAc/Toluene) to give the product as a yellow oil (206 mg, 0.951 mmol, 96%). Kugelrohr distillation (0.1 torr, 250 °C) gave the product as a colourless oil (191 mg, 0.883 mmol, 89%).
TLC (5% EtOAc/Toluene, UV/$KMnO_4$): 0.45; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 3H), 7.13 (m, 2H), 6.34 (s, 1H), 5.44 (s, 1H), 5.25 (s, 1H), 1.70 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 142.8, 136.9, 128.3, 128.2, 126.0, 125.9, 121.5, 86.3, 47.0, 33.6, 22.4, 8.5; IR (CH_2Cl_2 cast, cm^{-1}): 3034, 2969, 1765, 1655, 1604, 1106, 757, 701; HRMS (EI, *m/z*) Calcd for $C_{14}H_{16}O_2$: 216.11504. Found: 216.11490; Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.73; H, 7.47. Found: C, 78.07; H, 7.77.

3.3.1.8 (4R*, 5S*)-4-Ethyl -5-(4-methoxyphenyl)- 4-methyl-3-methylene -dihydro-furan-2-one 21h

Purified boronate **19e** (326 mg, 1.15 mmol) and *p*-methoxybenzaldehyde (138 mg, 1.01 mmol) in toluene (1 mL) were heated at 80 °C under Ar. After 60 h the mixture was concentrated and purified by flash chromatography (30 g silica, 25% Et_2O/Hexane) to give the product as a colourless oil (179 mg, 0.728 mmol, 72%). Kugelrohr distillation (0.1 torr, 250 °C) gave an analytically pure sample (176 mg, 0.713 mmol, 70%).
TLC (5% EtOAc/Toluene, UV/$KMnO_4$): 0.45; ^1H NMR (500 MHz, $CDCl_3$): δ 7.00 (AB, *J* = 8.3 Hz, 2H), 6.80 (AB, *J* = 8.8 Hz, 2H), 6.32 (s, 1H), 5.39 (s, 1H), 5.17 (s, 1H), 3.73 (s, 3H), 1.65 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 159.6, 143.1, 129.0, 127.3, 121.4, 113.7, 86.3, 55.2, 46.9, 33.5, 22.1, 8.4; IR (CH_2Cl_2 cast, cm^{-1}): 2967, 1765, 1657, 1612, 1106, 816; HRMS (EI, *m/z*) Calcd for $C_{15}H_{18}O_3$: 246.12560. Found: 246.12519; Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.38. Found: C, 72.82; H, 7.27.

3.3.1.9 (4R*, 5S*)-4-Ethyl -4-methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one 21i

Boronate **19e** (307 mg, 1.09 mmol) and *p*-nitrobenzaldehyde (95 mg, 0.63 mmol) in toluene (1 mL) were heated at 80 °C under Ar. After 5 d the reaction was concentrated and the residue was purified by flash chromatography (17 g silica, 5% EtOAc/Toluene) and then Kugelrohr distillation (0.1 torr, 225 °C) to give the product as an oil (133 mg, 0.508 mmol, 81%).

TLC (5% EtOAc/Toluene, UV/$KMnO_4$): 0.33; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (AB, J = 8.8 Hz, 2H), 7.35 (AB, J = 8.3 Hz, 2H), 6.40 (s, 1H), 5.51 (s, 1H), 5.35 (s, 1H), 1.75 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 148.0, 144.2, 141.9, 126.9, 123.7, 122.7, 84.6, 47.1, 33.3, 22.8, 8.5; IR (CH_2Cl_2 cast, cm^{-1}): 3083, 2970, 1771, 1653, 1607, 1521, 1349, 1103; HRMS (EI, *m/z*) Calcd for $C_{14}H_{15}NO_4$: 261.10010. Found: 261.10003; Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80; N, 5.36. Found: C, 63.98; H, 5.90; N, 5.13.

3.3.1.10 rac-3-(3-Butenyl)-4-methyl-5-(4-methoxyphenyl)-5H-furan-2-one 21j

A solution of boronate **19f** (143 mg, 0.511 mmol) and *p*-anisaldehyde (64 mg, 0.47 mmol) in toluene (1 mL) were heated at 110 °C for 16 h. The solvent was then removed and the residue purified by flash chromatography (25% Et_2O/Hexanes, 23 g silica) to give the title lactone as its [3+3] rearranged product (73 mg, 0.282 mmol, 60%). Kugelrohr distillation (250 °C, 0.1 torr) gave an analytical sample (59.2 mg, 0.23 mmol, 48%).

TLC (25% Et_2O/Hexanes, UV/$KMnO_4$): 0.17; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (AB, J = 8.7 Hz, 2H), 6.87 (AB, J = 8.6 Hz, 2H), 5.78 (dtt, J = 18.0 Hz, 9.0 Hz, 7.7 Hz, 1H), 5.53 (s, 1H), 5.04 (dd, J = 17.1 Hz, 1.4 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 3.79 (s, 3H), 2.40 (m, 2H), 2.32 (m, 2H), 1.77 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 160.2, 159.7, 137.2, 128.3, 126.7, 126.4, 115.8, 114.3, 84.8, 55.3, 32.1, 23.2, 12.4; IR (CH_2Cl_2 cast, cm^{-1}): 3071, 2931, 1773, 1660, 1607, 1105, 823, 741, 702; HRMS (EI, *m/z*) Calcd for $C_{16}H_{18}O_3$: 258.12558. Found:. 258.12529.

3.3.1.11 (4R, 5S*)-4-Butyl –4-methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one 21k*

Boronate **19g** (175 mg, 0.592 mmol) and *p*-nitrobenzaldehyde (77 mg, 0.51 mmol) in toluene (1 mL) were heated at 80 °C under Ar overnight. The mixture was then concentrated and purified by flash chromatography (14 g silica, 25% Et_2O/Hexane, pre-absorption) to give the product as a colourless oil (112 mg, 0.387 mmol, 76%). Kugelrohr distillation (0.1 torr, 225 °C) gave an analytically pure sample (112 mg, 0.387 mmol, 76%).

TLC (50% Et_2O/Hexane, UV/$KMnO_4$): 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (AB,

J = 8.6 Hz, 2H), 7.50 (AB, J = 8.6 Hz, 2H), 6.35 (s, 1H), 5.54 (s, 1H), 5.20 (s, 1H), 1.38 (s, 3H), 1.04 (m, 6H), 0.68 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 147.9, 142.6, 142.3, 127.0, 123.6, 122.1, 87.1, 47.1, 34.4, 24.9, 22.7, 21.4, 13.7; IR (CH_2Cl_2 cast, cm^{-1}): 2957, 1773, 1668, 1606, 1521, 1348; HRMS (EI, *m/z*) Calcd for $C_{16}H_{19}NO_4$: 289.13141. Found: 289.13071; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.63; N, 4.84. Found: C, 65.99; H, 6.72; N, 4.80.

3.3.1.12 (4R*, 5S*)–4-Methyl-3-methylene-5-(4-nitrophenyl)-4-phenyl-dihydro-furan-2-one 21l

Boronate **19h** (125 mg, 0.394 mmol) and *p*-nitrobenzaldehyde (62 mg, 0.41 mmol) in toluene (1 mL) were heated at 80 °C under Ar for 64 h. The mixture was then concentrated and purified by flash chromatography (25 g silica, 50% CH_2Cl_2/Hexane) to give the solid product (32 mg, 0.104 mmol, 26%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (AB, J = 8.9 Hz, 2H), 7.43 (m, 2H), 7.38 (m, 1H), 7.33 (m, 2H), 7.16 (AB, J = 8.6 Hz, 2H), 6.43 (s, 1H), 5.67 (s, 1H), 5.41 (s, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 147.8, 145.7, 142.0, 141.2, 129.0, 128.0, 127.4, 126.3, 123.8, 123.5, 87.7, 51.8, 22.1; Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.88; H, 4.90; N, 4.53. Found: C, 69.28; H, 4.99; N, 4.36.

3.3.1.13 (4R*, 5R*)-4-(tert-Butyldiphenylsilyloxymethyl)-4-methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one 21m

A solution of boronate **19i** (308 mg, 0.605 mmol) and *p*-nitrobenzaldehyde (90 mg, 0.59 mmol) in toluene (1 mL) were heated at 80 °C for 64 h. The solvent was then removed and the residue purified by flash chromatography (50% CH_2Cl_2/Hexanes, 25 g silica, pre-absorption) to give the title lactone (223 mg, 0.444 mmol, 75%). This compound was not sufficiently volatile for Kugelrohr distillation.

TLC (50% CH_2Cl_2/Hexanes, UV/$KMnO_4$): 0.22; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.9 Hz, 2H), 7.63 (m, 4H), 7.44 (m, 6H), 7.23 (d, J = 7.9 Hz, 2H), 6.39 (s, 1H), 5.64 (s, 1H), 5.48 (s, 1H), 3.72 (AB, J = 10.2 Hz, 1H), 3.54 (AB, J = 10.2 Hz, 1H), 1.10 (s, 9H), 0.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 147.8, 144.2, 140.1, 135.7, 135.6, 132.4, 132.3, 130.2, 130.1, 128.0, 127.9, 126.9, 123.6, 123.5, 82.7, 69.6, 48.8, 27.0, 20.2, 19.4; IR (CH_2Cl_2 cast, cm^{-1}): 3071, 2931, 1773, 1660, 1607, 1105, 823, 741, 702; HRMS (EI, *m/z*) Calcd for $C_{25}H_{22}NO_5Si$ (M^+-^{t}Bu): 444.12674. Found: 444.12487.

3.3.2 Enantioselective allylborations - Single auxiliary approach

3.3.2.1 Chiral alkynoates 26

3.3.2.1.1 2-Butynoic acid, (R)-pantolactone ester 26a

This compound was prepared in analogy to the procedure of Koh and co-workers.[39] A solution of 2-butynoic acid **25** (470 mg, 5.59 mmol), (*R*)-pantolactone **28a** (742 mg, 5.70 mmol), DCC (1.33 g, 6.45 mmol) and DMAP (105 mg, 0.857 mmol) in CH_2Cl_2 (75 mL) was stirred at RT under Ar for 2 d. The resulting orange mixture was diluted with water (100 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with $NaHCO_{3(aq)}$ (2 x 25 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated to give the crude product (2.09 g). Flash chromatography (25% EtOAc/Hexanes, 100 g SiO_2, pre-absorption) gave the pure product as an oil (0.98 g, 5.0 mmol, 89%). Kugelrohr distillation of a small amount (0.1 torr, 150 °C) gave an analytical sample which solidified over time.
mp 65-67 °C; $[\alpha]^{26}_D$ (+) 6.5 (*c* 3.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.36 (s, 1H), 4.06 (AB, *J* = 9.0 Hz, 1H), 3.98 (AB, *J* = 9.1 Hz, 1H), 2.01 (s, 3H), 1.20 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 152.3, 88.7, 76.2, 76.0, 71.3, 40.3, 23.0, 19.8, 3.9; IR (CH_2Cl_2 cast, cm^{-1}): 2970, 2236, 1792, 1720, 1248, 1096; HRMS (EI, *m/z*) Calcd for $C_{10}H_{12}O_4$, 196.07356, found 196.07383; Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2. Found: C, 60.94; H, 6.21.

3.3.2.1.2 2-Butynoic acid, (-)-borneol ester 26b

This compound was made in analogy to the procedure of Fonquerna and co-workers.[20] A solution of 2-butynoic acid **25** (500 mg, 5.95 mmol) and (-)-borneol **28b** (922 mg, 5.98 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C under Ar was treated dropwise with a solution of DCC (1.26 g, 6.11 mmol) and DMPA (8.7 mg, 0.071 mmol) in CH_2Cl_2 (7.5 mL). The resulting mixture was stirred at 0 °C for 4.5 h and then at RT for 2 h, after which time the mixture was filtered. The residue was washed with CH_2Cl_2 (6 x 5 mL) and the combined filtrates were concentrated to give an orange slush (1.45 g). Flash chromatography (5% Et_2O/Hexanes, 63 g silica, pre-absorption) gave the pure product as a colourless oil which solidified under vacuum (1.06 g, 4.78 mmol, 80%). Kugelrohr distillation of a small amount of the product (100 °C, 0.1 torr) gave an analytical sample.
mp 57-59 °C; $[\alpha]^{26}_D$ (-) 43.5 (*c* 1.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.93 (m, 1H), 2.34 (m, 1H), 1.97 (m, 4H), 1.78 (m, 2H), 1.34 (m, 2H), 1.01 (dd, *J* = 13.8 Hz, 3.5 Hz, 1H),

0.87 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.1, 84.8, 81.5, 72.8, 48.8, 47.8, 44.7, 36.4, 27.9, 27.0, 19.6, 18.7, 13.4, 3.7; IR (CH_2Cl_2 cast, cm^{-1}): 2955, 2244, 1708, 1261; HRMS (EI, *m/z*) Calcd for $C_{14}H_{20}O_2$, 220.14633, found 220.14604; Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.06; H, 9.17.

3.3.2.1.3 2-Butynoic acid, (R)-1-phenylethanol ester 26c

This compound was prepared according to the procedure described in Section 3.3.2.1.2, with 2-butynoic acid **25** (0.786 g, 9.35 mmol), (*R*)-1-phenylethanol **28c** (1.02 g, 8.33 mmol), DCC (1.90 g, 9.22 mmol) and DMAP (51 mg, 0.42 mmol). Work up gave a dark orange slush (1.98 g). Flash chromatography (5% Et_2O/Hexanes, 100 g silica, pre-absorption) gave the product (1.24 g, 6.59 mmol, 79%) as a colourless oil.

TLC (5% Et_2O/Hexanes, UV/$KMnO_4$): 0.24; $[\alpha]^{26}_D$ (+) 4.55 (*c* 4.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 5H), 5.32 (q, *J* = 6.6 Hz, 1H), 1.96 (s, 3H), 1.56 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9, 140.7, 128.5, 128.1, 126.1, 85.5, 73.9, 72.6, 22.0, 3.7; IR (CH_2Cl_2 cast, cm^{-1}): 2982, 2240, 1707, 1253, 750, 699; HRMS (EI, *m/z*) Calcd for $C_{12}H_{12}O_2$, 188.08372, found 188.08347; Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.61; H, 6.44. Found: C, 76.63; H, 6.45.

3.3.2.1.4 2-Butynoic acid, (-)-menthol ester 26d

This compound was prepared according to the procedure described in Section 3.3.2.1.2, with 2-butynoic acid **25** (0.516 mg, 6.14 mmol), (-)-menthol **28d** (948 mg, 6.07 mmol), DCC (1.24 g, 6.00 mmol) and DMAP (17.8 mg, 0.146 mmol) in CH_2Cl_2 (7.5 mL) except that the reaction was left to stir at RT for 7 d. Work up gave a dark orange slush (2.57 g, >100%). Flash chromatography (5% Et_2O/Hexanes, 70 g silica, pre-absorption) gave the pure product as a colourless oil which solidified under vacuum (1.05 g, 4.74 mmol, 78%). Kugelrohr distillation of a small amount of the product (100 °C, 0.1 torr) gave an analytical sample.

mp 36-38 °C; $[\alpha]^{26}_D$ (-) 65.8 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74 (dt, *J* = 10.9 Hz, 4.5 Hz, 1H), 1.94 (m, 4H), 1.65 (m, 2H), 1.41 (m, 2H), 1.05 (m, 2H), 0.88 (m, 8H), 0.74 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 84.8, 75.8, 72.7, 46.8, 40.6, 34.0, 31.3, 26.1, 23.2, 21.9, 20.6, 16.1, 3.7; IR (CH_2Cl_2 cast, cm^{-1}): 2956, 2243, 1706, 1455, 1387, 1256; HRMS (EI, *m/z*) Calcd for $C_{14}H_{22}O_2$, 222.16199, found 222.16378.

3.3.2.1.5 2-Butynoic acid, (-)-8-phenylmenthol ester 26e

A solution of 2-butynoic acid **25** (0.54 g, 6.4 mmol) and (-)-8-phenylmenthol **28e** (1.01 g, 4.36 mmol) in CH_2Cl_2 (4 mL) at –78 °C under Ar was treated dropwise with a solution of DCC (1.42 g, 6.89 mmol) and DMAP (100 mg, 0.824 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was left to slowly come to RT overnight. The mixture was then filtered, the residue was washed with CH_2Cl_2 (6 x 5 mL) and the combined filtrates were concentrated to give an orange slush (2.17 g). Flash chromatography (5% Et_2O/Hexanes, 100 g silica, pre-absorption) gave the pure product as a colourless oil (1.19 g, 3.99 mmol, 91%), which was further purified by Kugelrohr distillation (250 °C, 0.1 torr) to give the pure product as a white solid (1.15 g, 3.87 mmol, 89%).

$[\alpha]^{26}_{D}$ (+) 9.7 (*c* 2.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.16 (m, 1H), 4.85 (dt, *J* = 10.8 Hz, 4.6 Hz, 1H), 1.97 (m, 2H), 1.89 (s, 3H), 1.54 (m, 2H), 1.42 (m, 1H), 1.34 (s, 3H), 1.25 (s, 3H), 1.02 (m, 2H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 150.8, 128.1, 125.6, 125.1, 84.9, 76.2, 72.8, 50.6, 41.5, 40.0, 34.4, 31.4, 27.0, 26.8, 26.3, 21.7, 3.8; IR (CH_2Cl_2 cast, cm^{-1}): 2954, 2254, 1702, 1600, 1258, 751, 700; HRMS (EI, *m/z*) Calcd for $C_{20}H_{26}O_2$, 298.19327, found 298.19264; Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.48; H, 8.80. Found: C, 80.32; H, 8.92.

3.3.2.1.6 2-Butynoic acid, 8-β-naphthylmenthol ester 26f

This compound was prepared according to the procedure described in Section 3.3.2.1.2, with 2-butynoic acid **25** (181 mg, 2.16 mmol), 8-(β-naphthyl)-menthol **28f** (500 mg, 1.78 mmol), DCC (429 mg, 2.08 mmol) and DMAP (21 mg, 0.17 mmol) except the mixture was left to stir at RT for 60 h. Work up gave a dark orange slush (767 mg). Flash chromatography (10% Et_2O/Hexanes, 28 g silica, pre-absorption) gave the product (496 mg). The product was further purified by Kugelrohr distillation (0.1 torr, 250 °C) to give an white crystalline solid (466 mg, 1.34 mmol, 75%).

mp 149-150 °C; $[\alpha]^{26}_{D}$ (-) 55.2 (*c* 1.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (m, 3H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.53 (dd, *J* = 8.7 Hz, 2.0 Hz, 1 H), 7.42 (dt, *J* = 6.9 Hz, 1.2 Hz, 1H), 7.36 (dt, *J* = 6.9 Hz, 1.2 Hz, 1H), 4.92 (dt, *J* = 10.7 Hz, 4.4 Hz, 1H), 2.15 (m, 1H), 1.86 (m, 1H), 1.75 (qd, *J* = 13.6 Hz, 3.5 Hz, 1H), 1.64 (m, 1H), 1.46 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H), 1.14 (qd, *J* = 13.0 Hz, 3.5 Hz, 1H), 1.03 (q, *J* = 12.2 Hz, 1H), 0.90 (qd, *J* = 13.0 Hz, 3.4 Hz, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8, 148.7, 133.7, 131.6, 128.1, 127.4, 127.1, 125.5, 124.9, 124.8, 122.7, 84.9, 75.7, 72.2, 50.0, 41.5, 39.9, 34.5, 31.4, 28.0, 26.6, 24.6, 21.8, 3.2; IR (CH_2Cl_2 cast, cm^{-1}): 3025, 2954, 2244, 1701, 1600, 1260, 854, 817, 749; HRMS (EI, *m/z*) Calcd for $C_{24}H_{28}O_2$, 348.20892, found 348.20842; Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.70; H, 8.11. Found: C, 82.52; H, 8.19.

3.3.2.1.7 2-Butynoic acid, 8-(4-methoxyphenyl)menthol ester 26g

This compound was prepared according to the procedure described in Section 3.3.2.1.2, with 2-butynoic acid **25** (0.385 g, 4.58 mmol), 8-(4-methoxyphenyl)-menthol **28g** (1.11 g, 4.23 mmol), DCC (0.96 g, 4.67 mmol) and DMAP (15 mg, 0.12 mmol). Work up gave a dark orange slush. Flash chromatography (5% Et_2O/Hexanes, 55 g silica, pre-absorption) gave the solid product (896 mg, 2.73 mmol, 65%).

mp 89-92 °C; $[\alpha]^{26}_D$ (+) 4.36 (*c* 2.89, $CHCl_3$); IR (CH_2Cl_2 cast, cm^{-1}): 2954, 2243, 1701, 1610, 1258, 1066, 830; HRMS (EI, *m/z*) Calcd for $C_{21}H_{28}O_3$, 328.20386, found 328.20444; Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.78; H, 8.61. Found: C, 76.46; H, 8.75.

3.3.2.1.8 2-Butynoic acid, 8-(4-phenylphenyl)menthol ester 26h

This compound was prepared according to the procedure described in Section 3.3.2.1.2, with 2-butynoic acid **25** (149 mg, 1.77 mmol), 8-(4-phenylphenyl)-menthol **28h** (0.49 g, 1.6 mmol), DCC (0.36 g, 1.7 mmol) and DMAP (38 mg, 0.32 mmol) except that the mixture was left to stir at RT overnight. Work up gave a dark-orange slush (0.77 g). Flash chromatography (5% Et_2O/Hexanes, 100 g silica, pre-absorption) gave the product (0.24 g, 0.64 mmol, 35%), which was further purified by Kugelrohr distillation (0.1 torr, 250 °C) to give the product as a solid (146 mg, 0.389 mmol, 24%).

mp 148-149 °C; $[\alpha]^{26}_D$ (+) 41.4 (*c* 2.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (m, 2H), 7.54 (AB, *J* = 8.2 Hz, 2H), 7.39 (m, 2H), 7.35 (AB, *J* = 8.4 Hz, 2H), 7.28 (m, 1H), 4.89 (dt, *J* = 10.8 Hz, 4.6 Hz, 1H), 2.02 (m, 1H), 1.88 (m, 1H), 1.70 (s, 3H), 1.68 (m, 1H), 1.60 (m, 1H), 1.43 (m, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.05 (m, 2H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 150.0, 140.8, 137.7, 128.6, 126.9, 126.7, 126.5, 125.9, 84.8, 75.8, 72.6, 50.6, 41.6, 39.8, 34.5, 31.4, 27.4, 26.8, 25.8, 21.8, 3.7; IR (CH_2Cl_2 cast, cm^{-1}): 3028, 2955, 2243, 1701, 1599, 1259, 837, 767, 698; HRMS (EI, *m/z*) Calcd for $C_{26}H_{30}O_2$, 374.22458, found 374.22467; Anal. Calcd for $C_{26}H_{30}O_2$: C, 83.37; H, 8.09. Found: C, 82.36; H, 8.40.

3.3.2.1.9 2-Butynoic acid, 8-(3,5-dimethylphenyl)menthol ester 26i

This compound was prepared according to the procedure described in Section 3.3.2.1.2, with 2-butynoic acid **25** (186 mg, 2.22 mmol), 8-(3,5-dimethylphenyl)-menthol **28i** (462 mg, 1.77 mmol), DCC (0.47 g, 2.3 mmol) and DMAP (95 mg, 0.78 mmol) except the reaction was left to stir at RT for 36 h. Work up gave a dark orange slush (770 mg). Flash chromatography (5% Et_2O/Hexanes, 43 g silica, pre-absorption) followed by Kugelrohr distillation (0.1 torr, 250 °C) gave the product as a colourless oil (251 mg, 0.768 mmol, 43%).

$[\alpha]^{26}_D$ (+) 0.12 (*c* 1.65, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.86 (s, 2H), 6.77 (s, 1H), 4.82 (dt, *J* = 10.7 Hz, 4.4 Hz, 1H), 2.28 (s, 6H), 1.91 (s, 3H), 1.90 (m, 2H), 1.55 (m, 2H), 1.41 (m, 1H), 1.30 (s, 3H), 1.23 (s, 3H), 1.00 (m, 2H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.79 (m, 1H); IR (CH_2Cl_2 cast, cm^{-1}): 2953, 2243, 1703, 1599, 1388, 1370, 1258, 846, 710; HRMS (EI, *m/z*) Calcd for $C_{22}H_{30}O_2$, 326.22458, found 326.22343; Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.92; H, 9.28. Found: C, 80.61; H, 9.17.

3.3.2.2 Chiral allylboronates 27

3.3.2.2.1 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, (R)-pantolactone ester 27a

A slurry of $CuBr{\cdot}SMe_2$ (212 mg, 1.03 mmol) in THF (3 mL) at 0 °C under Ar was treated with MeLi (1.18 M in ether, 1.8 mL, 2.1 mmol). Once a colourless solution formed (~10 min) the mixture was chilled to –78 °C and treated via canula with a –78 °C solution of butynoate **26a** (206 mg, 1.05 mmol) in THF (0.5 mL + 0.5 mL canula rinse) After 1 h, the mixture was treated with HMPA (1.8 mL) and iodomethaneboronate **23** (917 mg, 3.42 mmol), stirred for 5 min and then placed in a 0 °C bath for 2 h.). After 5 minutes the mixture was brought to RT, left to stir for 2 h, and then reaction was quenched with $NH_4Cl_{(aq)}$ (10 mL). The layers were separated and the aqueous layer was extracted with ether (4 x 10 mL). The combined organic layers were washed with water (6 x 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated, yielding the crude boronate as a yellow oil (390 mg, >100%).

^1H NMR (300 MHz, $CDCl_3$): δ 5.43 (s, 1H), 4.02 (m, 2H), 2.11 (s, 3H), 1.93 (s, 2H), 1.82 (s, 3H), 1.30-1.12 (m, 18H + impurities); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.5, 167.3, 145.8, 122.2, 83.1, 76.0, 74.6, 40.1, 24.6, 24.2, 23.3, 22.8, 19.9; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.7; IR (CH_2Cl_2 cast, cm^{-1}): 2977, 1792, 1721, 1628, 1146; HRMS (EI, *m/z*) Calcd for $C_{18}H_{29}{}^{11}BO_6$, 352.20572, found 352.20556.

3.3.2.2.2 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, (-)-borneol ester 27b

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with (-)-borneol butynoate **26b** (232 mg, 1.05 mmol), CuBr·SMe_2 (217 mg, 1.06 mmol), MeLi (1.29 M in Et_2O, 1.6 mL, 2.1 mmol), and iodomethaneboronate **23** (842 mg, 3.14 mmol). Usual work-up gave the crude boronate as a yellow oil (453 mg, >100%).

^1H NMR (300 MHz, $CDCl_3$): δ 4.88 (m, 1H), 2.36 (m, 1H), 2.04 (s, 3H), 1.96 (m, 1H), 1.89 (br s, 2H), 1.76 (s, 3H), 1.72 (m, 1H), 1.66 (m, 1H), 1.24 (m, 2H), 1.20 (s, 12H), 1.01 (m, 1H), 0.90 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 141.9, 123.9, 83.0, 79.7, 48.6, 47.6, 44.8, 36.8, 28.0, 27.4, 24.7, 24.4, 23.0, 19.6, 18.8, 13.5; ^{11}B NMR (64 MHz, $CDCl_3$): δ 33.8; IR (CH_2Cl_2 cast, cm^{-1}): 2978, 1708, 1632, 1371, 1112; HRMS (EI, *m/z*) Calcd for $C_{22}H_{37}{}^{11}BO_4$, 376.27850, found 376.27917.

3.3.2.2.3 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, (R)-1-phenylethanol ester 27c

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with (*R*)-1-phenylethyl butynoate **26c** (621 mg, 3.30 mmol), CuBr·SMe_2 (6.91 mg, 3.36 mmol), MeLi (1.37 M in Et_2O, 4.8 mL, 6.5 mmol), and iodomethaneboronate **23** (1.9 mL, density = 1.4 g/mL, 9.9 mmol). Usual work-up gave the crude boronate as a yellow oil (1.12 g, 98%).

^1H NMR (200 MHz, $CDCl_3$): δ 7.30 (m, 5H), 5.94 (q, *J* = 7 Hz, 1H), 2.06 (s, 3H), 1.92 (br s, 2H), 1.80 (s, 3H), 1.57 (d, *J* = 7 Hz, 3H), 1.20 (s, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.2, 142.7, 142.2, 128.2, 127.4, 126.0, 123.6, 83.0, 71.8, 24.3, 23.1, 23.0, 22.5; ^{11}B NMR (64 MHz, $CDCl_3$): δ 31.7; IR (CH_2Cl_2 cast, cm^{-1}): 2978, 1711, 1634, 1347, 1146, 760, 699; HRMS (EI, *m/z*) Calcd for $C_{20}H_{29}{}^{11}BO_4$, 344.21588, found 344.21628.

3.3.2.2.4 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, (-)-menthol 27d

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with (-)-menthol butynoate **26d** (198 mg, 0.890 mmol), CuBr·SMe_2 (184 mg, 0.896 mmol), MeLi (1.29 M in Et_2O, 1.4 mL, 1.8 mmol), and iodomethaneboronate **23** (810 mg, 3.02 mmol). Usual work-up gave the crude boronate as a yellow oil (316 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (dt, *J* = 7.0 Hz, 4.5 Hz, 1H), 2.1-1.9 (m, 2H), 2.00 (s, 3H), 1.84 (br s, 2H), 1.75 (s, 3H), 1.7-1.3 (m, 4H), 1.19 (s, 12H), 1.1-0.8 (m, 3H), 0.86 (m, 6H), 0.73 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.0, 141.3, 124.1, 83.0, 73.7, 47.1, 41.0, 34.3, 31.4, 25.6, 24.5, 23.0, 21.8, 20.7, 15.8; ^{11}B NMR (64 MHz, $CDCl_3$): δ 31.6; IR (CH_2Cl_2 cast, cm^{-1}): 2956, 1708, 1643, 1347, 1108; HRMS (EI, *m/z*) Calcd for $C_{22}H_{39}{}^{11}BO_4$, 378.29413, found 378.29497.

3.3.2.2.5 *2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, (-)-8-phenylmenthol ester 27e*

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with (-)-8-phenylmenthol butynoate **26e** (311 mg, 1.04 mmol), CuBr·SMe_2 (212 mg, 1.04 mmol), MeLi (1.4 M in Et_2O, 1.5 mL, 2.1 mmol), and iodomethaneboronate **23** (0.60 mL, 3.1 mmol). Usual work-up gave the crude boronate as a yellow oil (511 mg). Flash chromatography (10% Et_2O/Hexanes, 23 g silica, pre-absorption) gave the purified compound as a colourless oil (209 mg, 0.460 mmol, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (m, 4H), 7.10 (m, 1H), 4.88 (dt, *J* = 10.7 Hz, 4.4 Hz, 1H), 1.94 (m, 2H), 1.93 (s, 3H), 1.72 (m, 5H), 1.55 (m, 1H), 1.42 (m, 2H), 1.32 (s, 3H), 1.25 (s, 3H), 1.22 (s, 12H), 0.98 (m, 2H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 151.1, 142.2, 127.7, 125.6, 124.9, 124.1, 83.0, 74.2, 51.0, 42.2, 40.2, 34.8, 31.4, 28.2, 27.2, 25.5, 25.0, 24.9, 23.5, 23.2, 21.9; ^{11}B NMR (64 MHz, $CDCl_3$): δ 34.9; IR (CH_2Cl_2 cast, cm^{-1}): 3056, 2952, 1701, 1631, 1600, 1347, 1147, 767, 700; HRMS (EI, *m/z*) Calcd for $C_{28}H_{43}{}^{11}BO_4$, 454.32544, found 454.32597.

3.3.2.2.6 *2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, 8-β–naphthylmenthol ester 27f*

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with 8-β-napthylmenthol butynoate **26f** (1.54 g, 4.42 mmol), CuBr·SMe_2 (917 mg, 4.46 mmol), MeLi (1.27 M in Et_2O, 7.0 mL, 8.9 mmol), and iodomethaneboronate **23** (3.91 g, 14.6 mmol). Usual work-up gave the crude boronate as a yellow oil (2.82 g, >100%). Flash chromatography (25% Et_2O/Hexanes) of a small aliquot gave an analytical sample as a white solid.

TLC (25% Et_2O/Hexanes, UV/$KMnO_4$): 0.47; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (m, 3H), 7.57 (s, 1H), 7.46 (dd, *J* = 8.7 Hz, 1.8 Hz, 1H), 7.36 (m, 2H), 4.92 (dt, *J* = 10.7 Hz, 4.3 Hz, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.75 (s, 3H), 1.58 (m, 2H), 1.48 (br s, 2H), 1.46 (s, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.19 (s, 12H), 1.09 (m, 1H), 0.98 (q,

J = 11.0 Hz, 1H), 0.84 (m, 1H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 149.0, 142.6, 133.3, 131.4, 127.9, 127.2, 127.1, 125.4, 125.0, 124.8, 123.7, 123.0, 83.0, 73.9, 50.5, 42.2, 40.2, 34.8, 31.4, 27.0, 26.6, 24.9, 24.8, 23.3, 23.1, 21.9; ^{11}B NMR (64 MHz, $CDCl_3$): δ 32.9; IR (CH_2Cl_2 cast, cm^{-1}): 3066, 2975, 1686, 1632, 1601, 1357, 1145, 876, 819, 749; HRMS (EI, *m/z*) Calcd for $C_{32}H_{45}{}^{11}BO_4$, 504.34109, found 504.34234.

3.3.2.2.7 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, 8-(4-methoxyphenyl)menthol ester 27g

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with 8-(4-anisyl)menthol butynoate **26g** (821 mg, 2.50 mmol), CuBr·SMe_2 (526 mg, 2.56 mmol), MeLi (1.37 M in Et_2O, 3.8 mL, 5.2 mmol), and iodomethaneboronate **23** (2.28 g, 8.51 mmol). Usual work-up gave the crude boronate as a yellow oil (1.68 g, >100%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (AB, J = 8.9 Hz, 2H), 6.76 (AB, J = 8.9 Hz, 2H), 4.85 (dt, J = 10.7 Hz, 4.4 Hz, 1H), 3.76 (s, 3H), 2.0-1.7 (m, 4H), 1.94 (s, 3H), 1.73 (s, 3H), 1.53 (m, 1H), 1.40 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H), 1.19 (s, 12H), 1.0-0.7 (m, 3H), 0.81 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3, 156.9, 143.2, 142.2, 126.6, 124.1, 113.0, 83.1, 74.3, 55.2, 51.1, 42.2, 39.6, 34.7, 31.4, 28.6, 27.2, 24.9, 24.8, 24.5, 23.3, 21.9; ^{11}B NMR (64 MHz, $CDCl_3$): δ 31.6; IR (CH_2Cl_2 cast, cm^{-1}): 2975, 1701, 1611, 1600, 1346, 1146, 830; HRMS (EI, *m/z*) Calcd for $C_{29}H_{45}{}^{11}BO_5$, 484.33600, found 484.33623.

3.3.2.2.8 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, 8-(4-phenylphenyl)menthol ester 27h

This compound was prepared according to the procedure described in Section 3.3.2.2.1, with 8-(4-phenylphenyl)menthol butynoate **26h** (146 mg, 0.389 mmol), CuBr·SMe_2 (80 mg, 0.39 mmol), MeLi (1.27 M in Et_2O, 0.61 mL, 0.77 mmol), and iodomethaneboronate **23** (477 mg, 1.78 mmol). Usual work-up gave the crude boronate as a yellow oil (250 mg, >100%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.6-7.3 (m, 9H), 4.80 (m, 1H), 2.1-1.9 (m, 2H), 1.94 (br s, 2H), 1.90 (s, 3H), 1.7-1.4 (m, 3H), 1.64 (s, 3H), 1.38 (s, 3H), 1.24 (s, 3H), 1.20 (s, 12H), 1.1-0.8 (s, 6H); ^{11}B NMR (64 MHz, $CDCl_3$): δ 31.6; IR (CH_2Cl_2 cast, cm^{-1}): 3027, 2962, 1702, 1599, 1343, 1144, 801, 767, 698; HRMS (EI, *m/z*) Calcd for $C_{34}H_{47}{}^{11}BO_4$, 530.35675, found 530.35769.

3.3.2.2.9 2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-3-methylbut-2-enoic acid, 8-(3,5-dimethylphenyl)menthol ester 27i

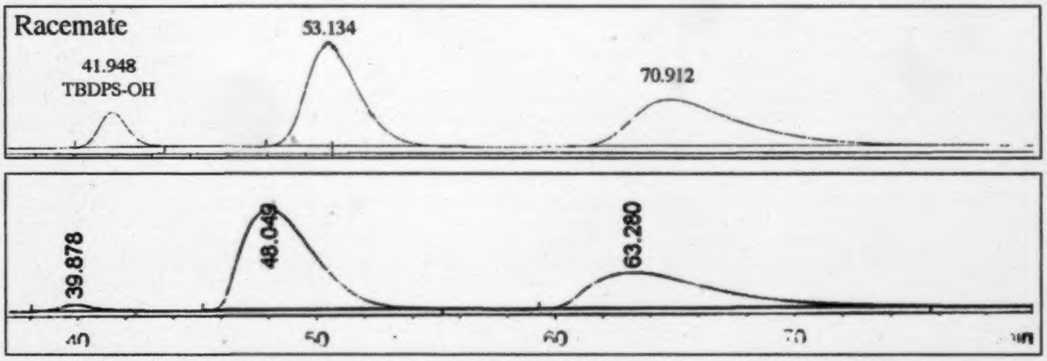
This compound was prepared according to the procedure described in Section 3.3.2.2.1, with 8-(3,5-dimethylphenyl)menthol butynoate **26i** (221 mg, 0.677 mmol), CuBr·SMe$_2$ (143 mg, 0.698 mmol), MeLi (1.27 M in Et$_2$O, 1.1 mL, 1.4 mmol), and iodomethaneboronate **23** (514 mg, 1.92 mmol). Usual work-up gave the crude boronate as a yellow oil (342 mg, >100%).

^{11}B NMR (64 MHz, CDCl$_3$): δ 31.4; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2922, 1704, 1633, 1599, 1343, 1145, 845, 710; HRMS (EI, *m/z*) Calcd for $C_{30}H_{47}{}^{11}BO_4$, 482.35675, found 482.35614.

3.3.2.3 Enantioenriched lactones from reaction with chiral boronates 27

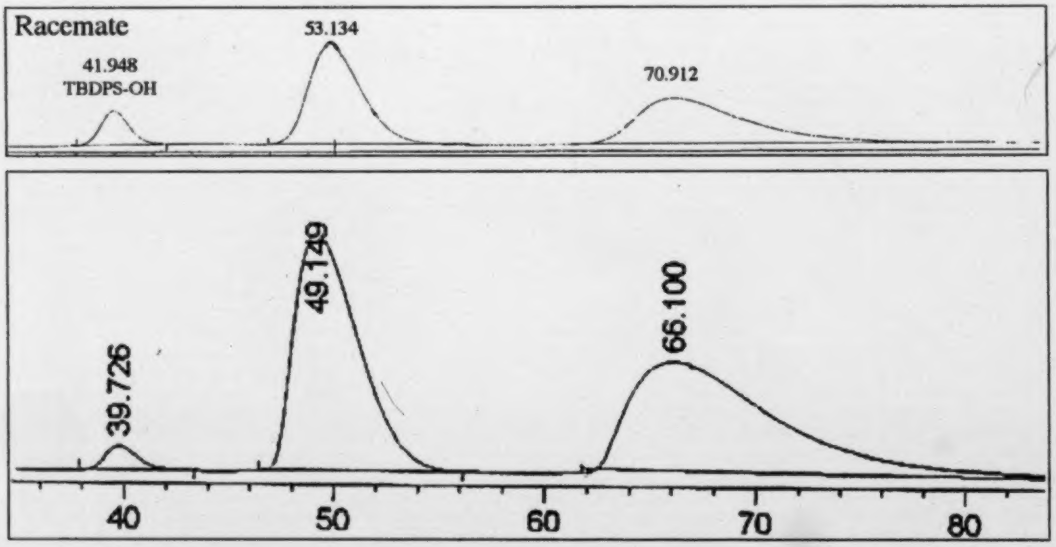
3.3.2.3.1 Allylboration with (R)-pantolactone derived 27a

Boronate **27a** (276 mg, 1.03 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (217 mg, 0.695 mmol) were stirred together at RT for 8 d. The mixture was then purified by flash chromatography (5% EtOAc/Toluene, 25 g silica) to give the enantioenriched lactone **30a** (190 mg, 0.466 mmol, 67%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 22% for the (*S*)-enantiomer.



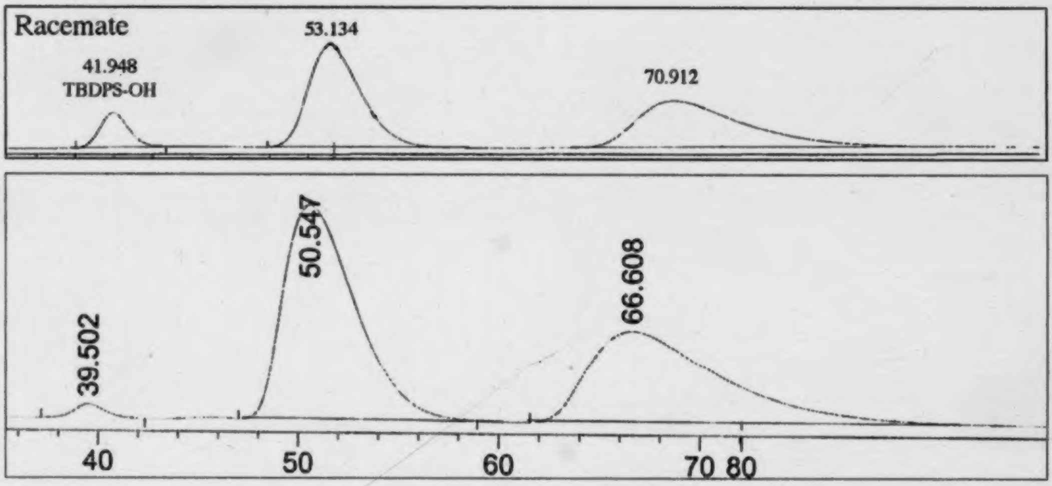
3.3.2.3.2 Allylboration with (-)-borneol derived 27b

Boronate **27b** (416 mg, 1.13 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (261 mg, 0.836 mmol) were stirred together at RT for 8 d. The mixture was then purified by flash chromatography (20% Et$_2$O/Hexanes, 20 g silica) to give the enantioenriched lactone **30b** (229 mg, 0.561 mmol, 64%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 6% for the (*R*)-enantiomer.



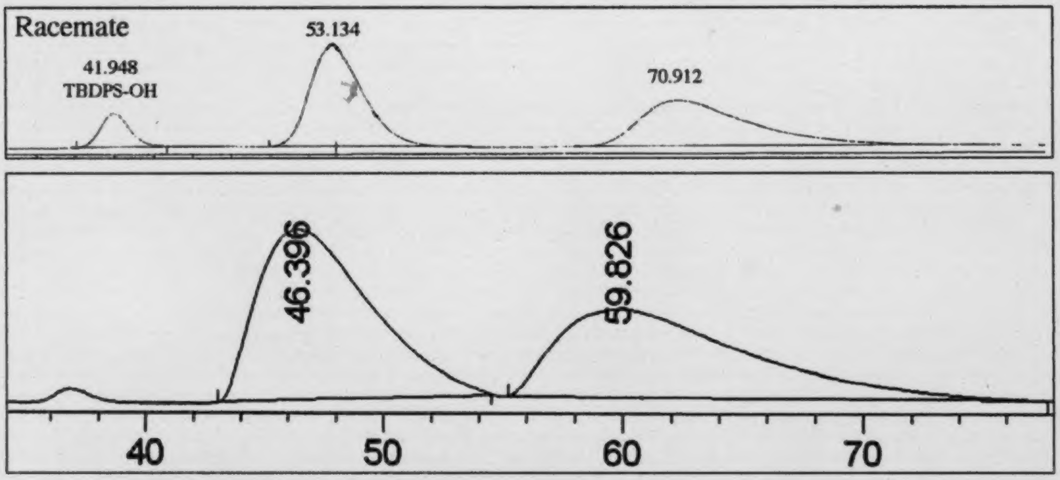
3.3.2.3.3 Allylboration with (R)-1-phenylethanol derived 27c

Boronate **27c** (520 mg, 1.51 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (325 mg, 1.04 mmol) were stirred together in toluene (1 mL) at RT for 26 d. The mixture was then purified by flash chromatography (5% EtOAc/Toluene, 25 g silica) to give the enantioenriched lactone **30c** (0.30 g, 0.734 mmol, 70%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 13% for the (*S*)-enantiomer.



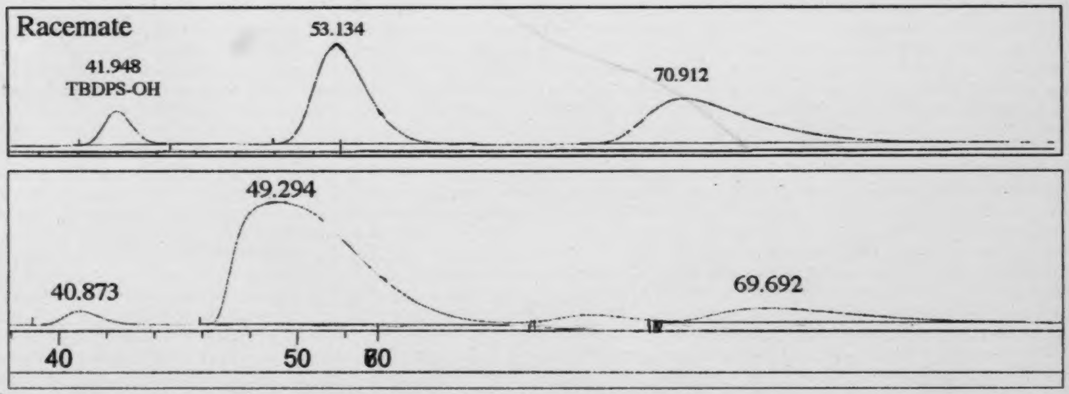
3.3.2.3.4 Allylboration with (-)-menthol derived 27d

Boronate **27d** (270 mg, 0.71 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (149 mg, 0.476 mmol) were stirred together at RT for 8 d. The mixture was then purified by flash chromatography (5% EtOAc/Toluene, 20 g silica) to give the enantioenriched lactone **30d** (150 mg, 0.367 mmol, 78%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 7% for the (*S*)-enantiomer.



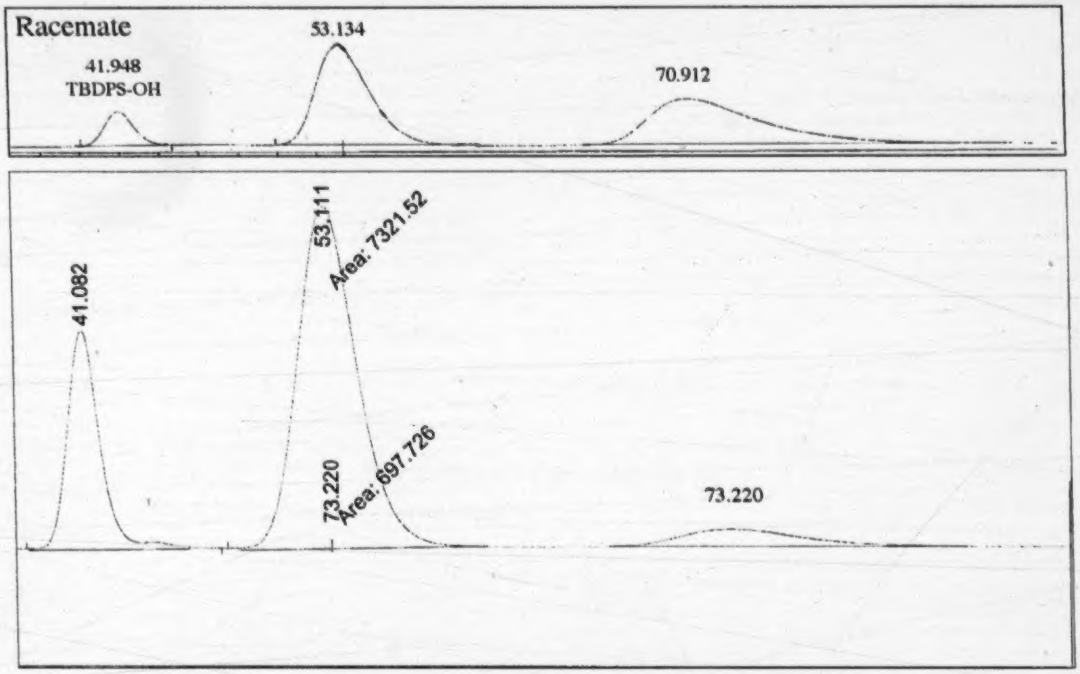
3.3.2.3.5 Allylboration with (-)-8-phenylmenthol derived 27e

Boronate **27e** (372 mg, 0.819 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (168 mg, 0.537 mmol) were stirred together in toluene (1 mL) at RT for 36 d. A spatula tip of pTSA was then added and the mixture was left to stir for 30 min. The reaction was then quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude lactone **30e**, which was then purified by flash chromatography to give the pure product (111 mg, 0.272 mmol, 51%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 80% for the (*S*)-enantiomer.



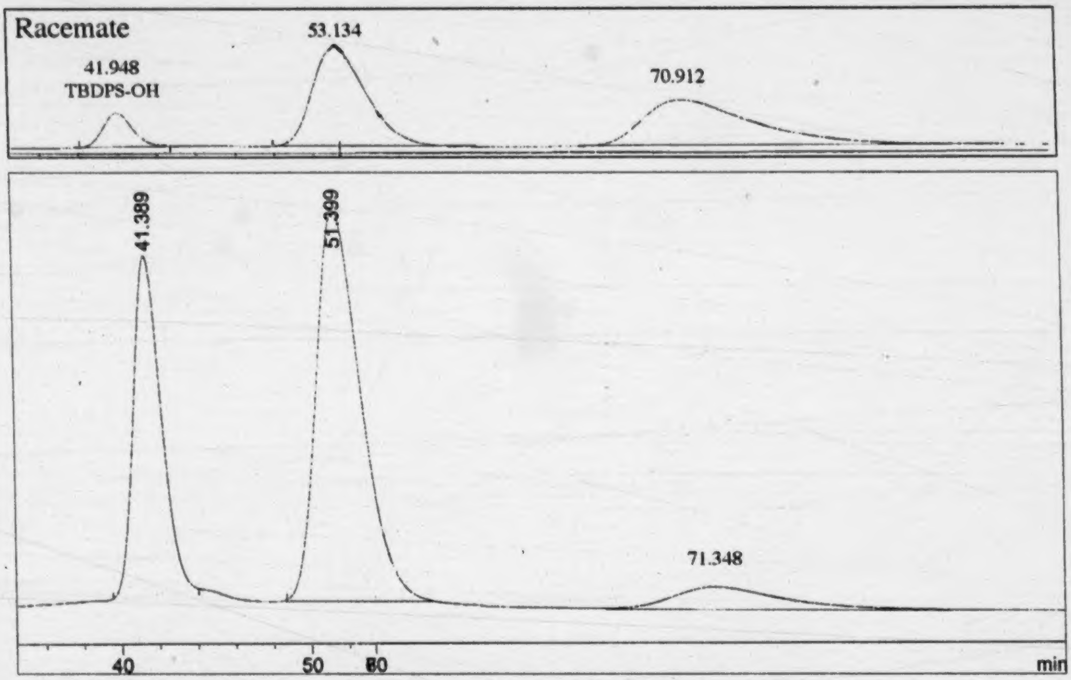
3.3.2.3.6 *Allylboration with β-naphthylmenthol derived 27f in toluene*

Boronate **27f** (565 mg, 1.12 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (243 mg, 0.778 mmol) were stirred together in toluene (1 mL) at RT for 15 d. A spatula tip of pTSA was then added and the mixture was left to stir for 30 min. The reaction was then quenched with NaHCO$_{3(aq)}$ (5 mL) and extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated to give the crude lactone **30f** (674 mg), which was then purified by flash chromatography (10% acetone/hexanes, 60 g silica) to give the compound still contaminated with the free arylmenthol (300 mg, 95%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 82% for the (*S*)-enantiomer.



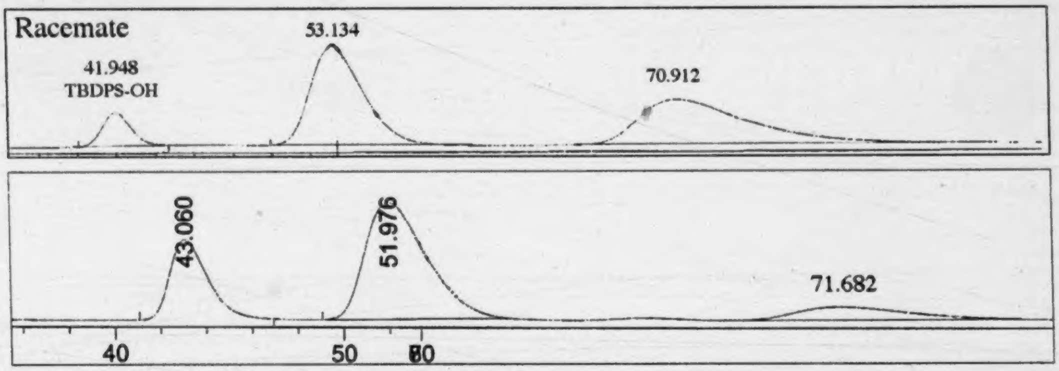
3.3.2.3.7 Allylboration with 8-β-naphthylmenthol derived 27f in CH_2Cl_2

Boronate **27f** (456 mg, 0.904 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (196 mg, 0.628 mmol) were stirred together in CH_2Cl_2 (1 mL) at RT for 14 d. A spatula tip of pTSA was then added and the mixture was left to stir for 30 min. The reaction was then quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude lactone **30f** (674 mg), which was then purified by flash chromatography (10% acetone/hexanes, 60 g silica) to give the compound still contaminated with the free arylmenthol (0.22 g, 86%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 75% for the (*S*)-enantiomer.



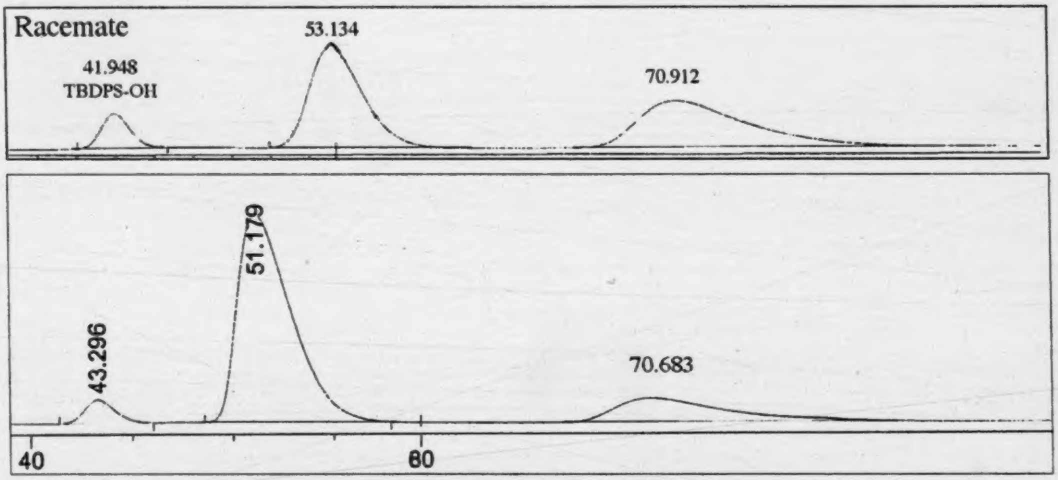
3.3.2.3.8 *Allylboration with 8-(4-methoxyphenyl)menthol derived 27g*

Boronate **27g** (515 mg, 1.06 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (230 mg, 0.737 mmol) were stirred together in toluene (1 mL) at RT for 14 d. A spatula tip of pTSA was then added and the mixture was left to stir for 4 h. The reaction was then quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude lactone **37g** (571 mg), which was then purified by flash chromatography (5% EtOAc/toluene, 25 g silica) to give the pure compound (223 mg, 0.547 mmol, 74%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 56% for the (*S*)-enantiomer.



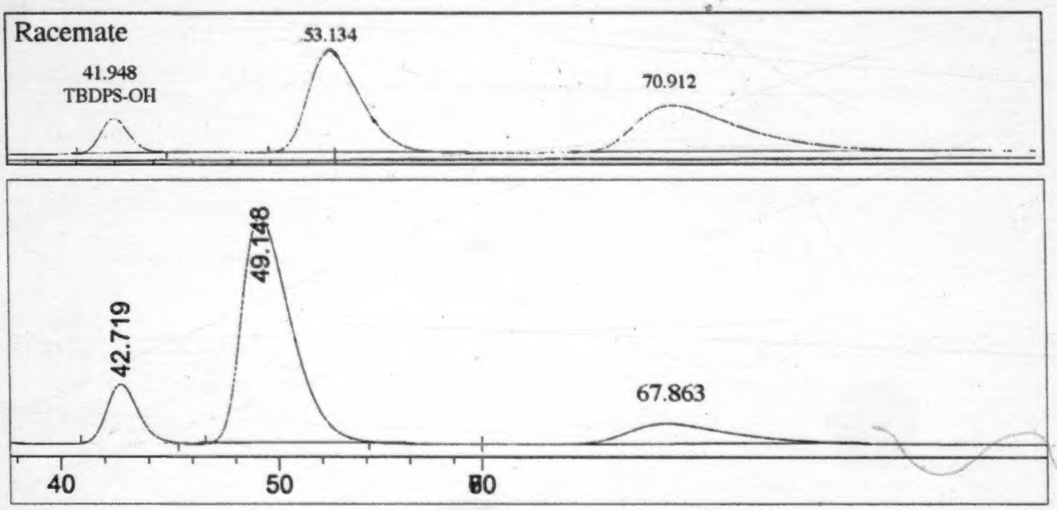
3.3.2.3.9 Allylboration with 8-(4-phenylphenyl)menthol derived 27h

Boronate **27h** (250 mg, 0.472 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (104 mg, 0.333 mmol) were stirred together in toluene (1 mL) at RT for 24 d. A spatula tip of pTSA was then added and the mixture was left to stir for 30 min. The reaction was then quenched with NaHCO$_{3(aq)}$ (5 mL) and extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated to give the crude lactone **30h**, which was then purified by flash chromatography (40% CH$_2$Cl$_2$/Hexanes, 35 g silica) to give the pure compound (33 mg, 0.081 mmol, 24%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 66% for the (*S*)-enantiomer.



3.3.2.3.10 Allylboration with 8-(3,5-dimethylphenyl)menthol derived 27i

Boronate **27i** (342 mg, 0.708 mmol) and 3-(*tert*-butyldiphenylsilyloxy)propanal **29** (147 mg, 0.470 mmol) were stirred together in toluene (0.5 mL) at RT for 15 d. A spatula tip of pTSA was then added and the mixture was left to stir for 30 min. The reaction was then quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude lactone **30i** (78 mg), which was then purified by flash chromatography (5% EtOAc/toluene, 11 g silica) to give the compound still contaminated with the free arylmenthol (78 mg, 41%). A second chromatography step (40% CH_2Cl_2/Hexanes, 5 g silica) gave the pure compound (11 mg, 0.026 mmol, 6%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 62% for the (*S*)-enantiomer.



3.3.3 Enantioselective allylborations - Dual auxiliary approach

3.3.3.1 *(1R, 2R, 3R, 4S)-4-Iodomethyl-1,10,10-trimethyl-2-phenyl-3,5-dioxa-4-bora-tricyclo[5.2.1.$0^{0,0}$]decane 34*

A solution of diisopropyl bromomethaneboronate **32a** (1.30 g, 5.84 mmol) in THF (20 mL) was treated with diol (-)-**18** (1.22 g, 4.96 mmol) and stirred under Ar overnight. In the morning the solvents were removed by distillation under Ar (bath temperature 110 °C) to give the crude bromomethaneboronate **33** as a brown oil. This oil was dissolved in acetone (10 mL), treated with NaI (1.58 g, 10.6 mmol) and refluxed for 60 h. The mixture was then filtered and concentrated by rotor evaporator. The residue taken up in CH_2Cl_2 (50 mL), filtered, and concentrated again to give the crude product (2.08 g). Kugelrohr distillation (150 °C, 0.1 torr) removed a volatile impurity. Continued distillation at 250 °C gave the pure product as a slightly coloured oil (1.57 g, 3.96 mmol, 80%).

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40 (m, 2H), 7.32 (m, 2H), 7.27 (m, 1H), 4.79 (s, 1H), 2.16 (m, 3H), 1.82 (m, 1H), 1.24 (s, 3H), 1.18 (m, 2H), 1.03 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 141.0, 127.5, 127.4, 126.6, 97.0, 89.5, 52.1, 50.4, 48.7, 29.5, 24.7, 23.5, 21.4, 9.3; ^{11}B NMR (64 MHz, CDCl$_3$): δ 32.4.

3.3.3.2 Dual auxiliary boronates 31a and 31b

A slurry of CuBr·SMe$_2$ (422 mg, 2.05mmol) in THF (3 mL) at 0 °C under Ar was treated with MeLi (1.4 M in Et$_2$O, 2.9 mL, 4.1 mmol). Once the colourless solution formed (~ 10 min) the flask was placed in a –78 °C bath and treated via canula with a pre-cooled solution of chiral alkynoate **26e** (604 mg, 2.02 mmol) in THF (1 mL, + 1 mL canula rinse) and left to stir for 1.5 h. The resulting dark mixture was then treated with the diisopropyl iodomethaneboronate **32b** (1.59 g, 5.90 mmol) and HMPA (3.6 mL), left to stir for 5 min and then stirred at 0 °C for 2 h. The reaction was then quenched with NH$_4$Cl$_{(aq)}$ (20 mL) and the resulting biphasic mixture was divided into two roughly equal portions. One portion was poured into a solution of diol (-)-**18** (250 mg, 1.02 mmol) in Et$_2$O (10 mL) and stirred for 30 min at RT. The layers were then separated and the aqueous phase was extracted with Et$_2$O (3 x 10 mL). The combined organic phases were washed with water (6 x 10 mL), brine (10 mL), dried (Na$_2$SO$_4$) and concentrated to give the crude product (722 mg). Flash chromatography (10% Et$_2$O/Hexanes) gave the purified boronate **31a** as a white solid (511 mg, 0.877 mmol). The second portion of the initial biphasic mixture was treated similarly with a solution of the enantiomeric diol (+)-**18** (254 mg, 1.03 mmol) to give the diastereomeric boronate **31b** (353 mg, 0.606 mmol) as a colourless syrup after chromatography. The combined yield for the two isomers was 864 mg (1.48 mmol, 73%).

(1*R*, 2*R*, 3*R*, 4*S*)-3-Methyl-2-(1,10,10-trimethyl-2-phenyl-3,5-dioxa-4-bora-tricyclo[5.2.1.0^{0,0}]dec-4-ylmethyl)-but-2-enoic acid, (1*R*, 2*S*, 3*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester 31a: mp = 50-55 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.43 (m, 2H), 7.33 (m, 2H), 7.23 (m, 3H), 7.13 (m, 3H), 4.68 (dt, *J* = 10.7 Hz, 4.3 Hz, 1H), 4.63 (s, 1H), 2.09 (d, *J* = 5.2 Hz, 1H), 2.05 (s, 3H), 1.9-1.3 (m, 6H), 1.70 (s, 3H), 1.3-1.0 (m, 4H), 1.20 (s, 3H), 1.19 (s, 3H), 1.12 (s, 3H), 1.0-0.8 (m, 2H), 0.93 (s, 3H), 0.90 (s, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.46 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.4, 151.2, 144.3, 141.9, 128.0, 127.7, 127.5, 127.2, 126.9, 125.6, 125.5, 125.0, 123.5, 95.7, 88.6, 73.9, 52.0, 48.9, 41.5, 39.9, 34.1, 31.2, 29.6, 28.3, 26.9, 25.2, 24.8, 23.7, 23.6, 23.1, 21.7, 20.8, 9.4; ^{11}B NMR (64 MHz, CDCl$_3$): δ 33.2; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 3056, 2953, 1704, 1628, 1600, 1350, 1122, 760, 701; HRMS (EI, *m/z*) Calcd for C$_{38}$H$_{51}$^{11}BO$_4$, 582.38806, found 582.38910.

(1*S*, 2*S*, 3*S*, 4*R*)-3-Methyl-2-(1,10,10-trimethyl-2-phenyl-3,5-dioxa-4-bora-tricyclo[5.2.1.$0^{0,0}$]dec-4-ylmethyl)-but-2-enoic acid, (1*R*, 2*S*, 3*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl ester 31b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (m, 2H), 7.30 (m, 2H), 7.3-7.1 (m, 6H), 4.75 (dt, *J* = 10.8 Hz, 4.3 Hz, 1H), 4.70 (s, 1H), 2.10 (d, *J* = 5.2 Hz, 1H), 1.94 (s, 3H), 1.8-0.8 (m, 12H), 1.69 (br s, 2H), 1.66 (s, 3H), 1.21 (s, 3H), 1.16 (s, 6H), 0.92 (s, 3H), 0.91 (s, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 150.8, 141.6, 141.1, 128.8, 128.0, 127.5, 127.2, 127.0, 126.5, 125.4, 124.8, 123.7, 95.6, 89.3, 88.5, 73.9, 51.9, 50.3, 50.0, 48.8, 41.6, 40.0, 34.4, 31.2, 29.6, 28.5, 27.0, 24.8, 23.6, 22.8, 21.8, 20.9, 9.4; ^{11}B NMR (64 MHz, $CDCl_3$): δ 35.4; IR (CH_2Cl_2 cast, cm^{-1}): 3056, 2955, 1704, 1600, 1346, 1121, 759, 701; HRMS (EI, *m/z*) Calcd for $C_{38}H_{51}{}^{11}BO_4$, 582.38806, found 582.38846.

3.3.3.3 (1R, 2R, 3R, 4S)-3-Methyl-2-(1,10,10-trimethyl-2-phenyl-3,5-dioxa-4-bora-tricyclo[5.2.1.$0^{0,0}$]dec-4-ylmethyl)-but-2-enoic acid, ethyl ester 37

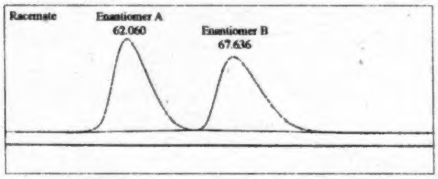
A slurry of $CuBr{\cdot}SMe_2$ (738 mg, 3.59 mmol) in THF (10.5 mL) at 0 °C under Ar was treated with MeLi (1.45 M in Et_2O, 4.9 mL, 7.1 mmol). Once the colourless solution formed (~ 10 min) the flask was placed in a –78 °C bath and treated via canula with a pre-cooled solution of ethyl 2-butynoate (400 mg, 3.56 mmol) in THF (1.8 mL, + 1.8 mL canula rinse) and left to stir for 1 h. The resulting dark mixture was then treated with the diisopropyl iodomethaneboronate **32b** (2.07 g, 7.67 mmol) and HMPA (5.6 mL, 32 mmol), left to stir for 5 min and then stirred at RT for 2 h. The reaction was then quenched with $NH_4Cl_{(aq)}$ (30 mL) and treated directly with a solution of diol (-)-**18** (873 mg, 3.54 mmol) in Et_2O (30 mL). The biphasic mixture was left to stir under Ar at RT for 2 h, the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined ether layers were washed with water (6 x 30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated to give the crude product (1.61 g). Flash chromatography (10% Et_2O/Hexanes, 106 g silica) gave the pure compound (646 mg, 1.63 mmol, 46%).

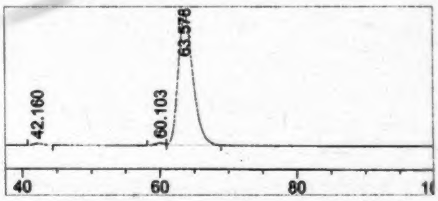
TLC (25% Et_2O/Hexanes, UV/$KMnO_4$): 0.56; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (m, 2H), 7.30 (m, 2H), 7.26 (m, 1H), 4.69 (s, 1H), 3.86 (m, 1H), 3.73 (m, 1H), 2.11 (d, *J* = 5.2 Hz, 1H), 2.02 (s, 3H), 1.86 (br s, 2H), 1.80 (m, 1H), 1.72 (s, 3H), 1.20 (s, 3H), 1.15 (m, 2H), 1.01 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 142.8, 141.8, 127.3, 127.1, 126.7, 123.3, 95.6, 88.8, 59.7, 51.9, 50.1, 48.9, 29.6, 24.7, 23.6, 23.0, 22.9, 20.7, 13.9, 9.3; ^{11}B NMR (64 MHz, $CDCl_3$): δ 33.2; IR (CH_2Cl_2 cast, cm^{-1}): 2956, 1713, 1633, 1345, 1121, 759, 702; HRMS (EI, *m/z*) Calcd for $C_{24}H_{33}{}^{11}BO_4$, 396.24719, found 396.24821.

3.3.3.4 *Preparation of enantioenriched lactones 36*

3.3.3.4.1 *Enantioenriched 4,4-Dimethyl-3-methylene-5-nonyl-dihydro-furan-2-one 36a from dual auxiliary boronate 31a – Matched Case*

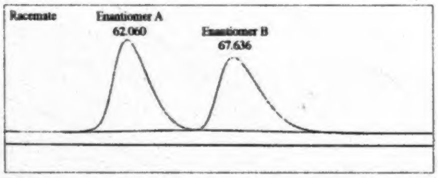
Boronate **31a** (213 mg, 0.366 mmol) and decanal (50 mg, 0.32 mmol) were stirred together in toluene (0.6 mL) at RT for 18 d. A spatula tip of pTSA was then added and the mixture was left to stir for 3 h. The reaction was then quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude lactone **36a** (240 mg), which was then purified by flash chromatography (1% EtOAc/toluene, 28 g silica) to give the pure compound (73 mg, 0.29 mmol, 90%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 98% for the (*S*)-enantiomer.

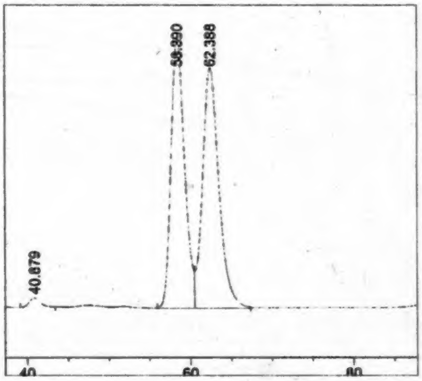




3.3.3.4.2 *Enantioenriched 4,4-Dimethyl-3-methylene-5-nonyl-dihydro-furan-2-one 36a from dual auxiliary boronate 31b – Mis-matched Case*

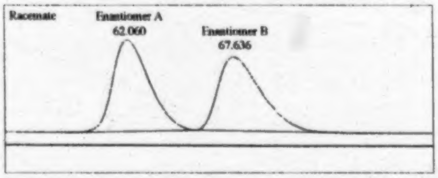
This reaction was carried out as described in Section 3.3.3.4.1 with boronate **31b** (306 mg, 0.524 mmol) and decanal (82 mg, 0.52 mmol) to give 20 mg of lactone **36a** (0.079 mmol, 15%). Chiral HPLC (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min) showed that the product was essentially racemic.

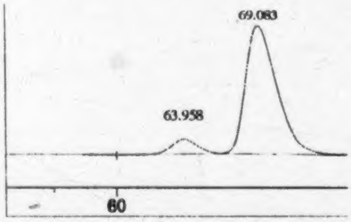




3.3.3.4.3 Enantioenriched 4,4-Dimethyl-3-methylene-5-nonyl-dihydro-furan-2-one 36a from β-naphthylmenthol boronate 27f

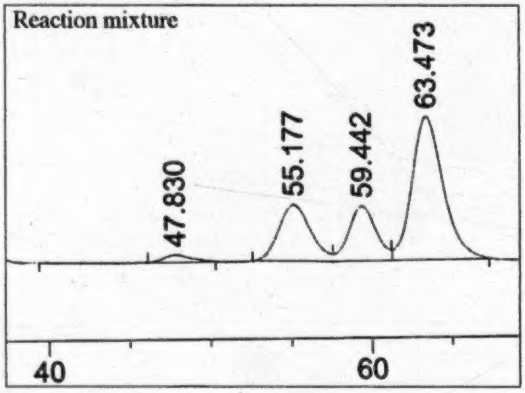
This reaction was carried out as described in Section 3.3.3.4.1 with boronate **27f** (402 mg, 0.797 mmol) and decanal (85 mg, 0.54 mmol) to give 28 mg of lactone **36a** (0.11 mmol, 20%). Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 82% for the (*S*)-enantiomer.

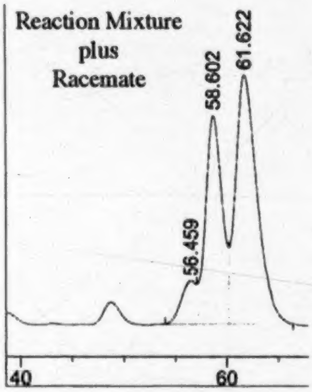




3.3.3.4.4 Enantioenriched 4,4-Dimethyl-3-methylene-5-nonyl-dihydro-furan-2-one 36a from chiral boronate 37

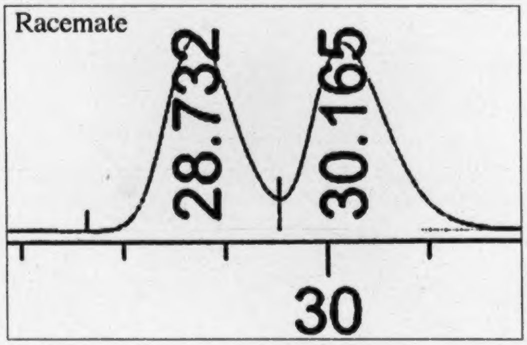
This reaction was carried out as described in Section 3.3.3.4.1 with boronate **37** (136 mg, 0.354 mmol) and decanal (42 mg, 0.27 mmol). The enantiomeric excess was determined from the crude product **36a**, resulting in a chromatogram with three peaks in the region of interest. The peaks due the two enantiomers of the product were identified by co-injecting the product from the reaction with a sample of the racemate. Enantiomeric excess (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min): 51% for the (*S*)-enantiomer.

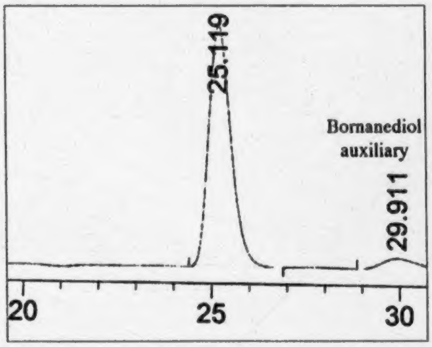




3.3.3.4.5 Enantioenriched 4,4-Dimethyl-3-methylene-5-phenyl-dihydro-furan-2-one 36b from dual auxiliary boronate 31a

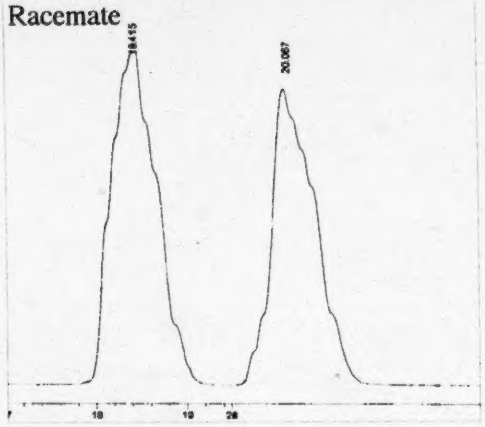
This reaction was carried out as described in Section 3.3.3.4.1 with boronate **31a** (172 mg, 0.295 mmol) and benzaldehyde (32 mg, 0.30 mmol). Flash chromatography (2.5% EtOAc/Toluene, 30 g silica) gave the product **36b** that was contaminated with both auxiliaries (33 mg, 55%). Enantiomeric excess (CHIRALCEL OD, 0.5% isopropanol/pentane, 1 mL/min): >95% for the (*S*)-enantiomer. The preparation of the racemate is described in Section 3.3.1.2 (page 70).

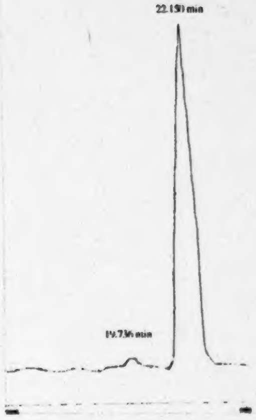




3.3.3.4.6 Enantioenriched 5-(4-Bromophenyl)-4,4-dimethyl-3-methylene-dihydro-furan-2-one 36c from dual auxiliary boronate 31a

This reaction was carried out as described in Section 3.3.3.4.1 with boronate **31a** (98 mg, 0.168 mmol) and *p*-bromobenzaldehyde (48 mg, 0.26 mmol). Work-up gave the crude product as an oil (100 mg). Flash chromatography (1% EtOAc/Toluene, 13 g silica) gave a small fraction of the pure product **36b** (5 mg) and another fraction of product that was contaminated with 8-phenylmenthol (15 mg). Total yield: 20 mg, 0.068 mmol, 40%. The contaminated product was dissolved in pentane and chilled in the freezer to produce X-ray quality crystals. Enantiomeric excess (CHIRALCEL OD, 2% isopropanol/hexane, 1 mL/min): >95% for the (*S*)-enantiomer. The preparation of the racemate is described in Section 4.5.4.8 (page 144).





3.3.4 Further transformations of lactones 21

3.3.4.1 α-Methylbutyrolactones 39 via hydrogenation of the exocyclic double bond

3.3.4.1.1 (3R*, 4R*, 5S*)-4-Ethyl-3,4-dimethyl-5-phenethyl-dihydro-furan-2-one 39a

This product was prepared by Melissa Chee. A solution of lactone **21b** (448 mg, 1.82 mmol) in EtOH (18 mL) was hydrogenated at 1 atm with 10% Pd/C (50 mg). After 6 h the mixture was filtered through Celite® and the residue was washed with ethanol (5 x 20 mL). The combined filtrates were concentrated and the resulting oil was purified by Kugelrohr distillation (250 °C, 0.1 torr) to give the product as a white solid (393 mg, 1.60 mmol, 80%).

TLC (10% EtOAc/Hexanes, $KMnO_4$): 0.25; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2 (m, 5H), 4.0 (dd, *J* = 11.1 Hz, 2.1 Hz, 1H), 2.9 (m, 1H), 2.7 (m, 1H), 2.45 (q, *J* = 14.4 Hz, 1H), 1.8 (m, 2H), 1.4 (m, 2H), 1.05 (d, *J* = 15 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.8 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7, 141.1, 128.5, 128.4, 126.1, 84.6, 45.1, 44.7, 32.9, 31.3, 29.8, 14.3, 9.0, 8.9; IR (CH_2Cl_2 cast, cm^{-1}): 3084, 2979, 1755; HRMS (EI, *m/z*) Calcd for $C_{16}H_{22}O_2$: 246.16198. Found: 246.16177; Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.02. Found: C, 77.76; H, 9.22.

3.3.4.1.2 (3R*, 4R*, 5S*)-4-Ethyl-3,4-dimethyl-5-nonyl-dihydro-furan-2-one 39b

This compound as prepared according to the procedure in Section 3.3.4.1.1, using lactone **21f** (107 mg, 0.401 mmol) and 10% Pd/C (18 mg) except the reaction was left overnight. Kugelrohr distillation (200 °C, 0.1 torr) afforded the pure product (92 mg, 0.34 mmol, 85%).

^{1}H NMR (500 MHz, CDCl$_3$): δ 3.99 (dd, *J* = 10.1 Hz, 2.6 Hz, 1H), 2.46 (q, *J* = 7.2 Hz, 1H), 1.58 (m, 1H), 1.46 (m, 3H), 1.25 (m, 12H), 1.2-0.8 (m, 5H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.8, 86.0, 45.3, 44.8, 31.9, 30.0, 29.6, 29.5, 29.4, 29.3, 27.1, 22.7, 14.4, 14.2, 9.1, 9.0; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2925, 1776, 1204; HRMS (EI, *m/z*) Calcd for $C_{17}H_{32}O_2$: 268.24023. Found: 268.23970; Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.04; H, 12.04. Found: C, 76.12; H, 12.13.

3.3.4.1.3 (3R*, 4R*, 5R*)-4-Ethyl-3,4-dimethyl-5-phenyl-dihydro-furan-2-one 39c

This compound as prepared according to the procedure in Section 3.3.4.1.1, using lactone **21g** (106 mg, 0.491 mmol) and 10% Pd/C (11 mg), except the reaction was left for 5 d. Kugelrohr distillation (250 °C, 0.1 torr) afforded the pure product (92 mg, 0.42 mmol, 86%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34 (m, 3H), 7.25 (m, 2H), 5.16 (s, 1H), 2.71 (q, *J* = 7.2 Hz, 1H), 1.56 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.54 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.6, 135.0, 128.08, 128.06, 126.2, 85.6, 47.5, 43.8, 29.0, 16.0, 9.5, 8.8; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 3032, 2971, 1782, 1658, 1134, 742, 701; HRMS (EI, *m/z*) Calcd for $C_{14}H_{18}O_2$: 218.13068. Found: 218.12994; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.01; H, 8.33. Found: C, 75.71; H, 8.19.

3.3.4.1.4 (3R*, 4S*, 5R*)-4-(2-Methylpropyl)-5-(4-methoxyphenyl)-3,4-dimethyl-dihydro-furan-2-one 39d

This compound as prepared according to the procedure in Section 3.3.4.1.1, using lactone **21e** (48 mg, 0.18 mmol) and 10% Pd/C (12 mg) except the reaction was left for 48 h. Kugelrohr distillation (250 °C, 0.1 torr) afforded the pure solid product (39 mg, 0.14 mmol, 81%).

TLC (25% Et$_2$O/Hexanes, PMA): 0.21; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.21 (AB, *J* = 8.6 Hz, 2H), 6.88 (AB, *J* = 8.7 Hz, 2H), 4.97 (s, 1H), 3.80 (s, 3H), 2.50 (q, *J* = 7.2 Hz, 1H), 1.26 (s, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.1-0.9 (m, 3H), 0.71 (d, *J* = 6.4 Hz, 3H), 0.54 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 178.4, 159.4, 127.3, 127.2, 113.6, 89.1, 55.3, 49.2, 48.4, 37.4, 25.3, 25.1, 23.6, 21.9, 9.4; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2958, 1778, 1613, 1385, 1367, 1252, 829; HRMS (EI, *m/z*) Calcd for $C_{17}H_{24}O_3$: 276.17255. Found: 276.17279; Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.86; H, 8.77. Found: C, 73.46; H, 8.93.

3.4 References

(1) For reviews, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2001**, pp 299-401; (b) Roush, W. R. In *Stereoselective Synthesis: Methods of Organic Chemistry (Houben-Weyl), 4th Ed.;* Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, **1995**; Vol. E21b, pp 1410-1486.; (c) Matteson, D. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin Heidelberg, **1995**; 260-328; (d) Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555-566.

(2) For some recent examples, see: (a) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737-1739; (b) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 681-684; (c) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513-3516; (d) Vidya, R.; Eggen, M.; Georg, G. I.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 757-760; (e) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981-6990; (f) Giordano, A.; Spinella, A.; Sodano, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1851-1854.

(3) Hoffmann, R. W.; Schlapbach, A. *Liebigs. Ann. Chem.* **1990**, 1243-1248.

(4) Sato, M.; Yamamoto, Y.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7071-7074.

(5) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868-1874.

(6) Nyzam, V.; Belaud, C.; Villiéras, J. *Tetrahedron Lett.* **1993**, *34*, 6899-6902. See also Chapter 2 of this thesis.

(7) Hoffmann, R. W.; Schlapbach, A. *Liebigs Ann. Chem.* **1991**, 1203-1206.

(8) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, *122*, 1783-1789.

(9) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190; (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Haltermam, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348; (c) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359; (d) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692-10697.

(10) Yamamoto, Y.; Hara, S.; Suzuki, A. *Synlett* **1996**, 883-884.

(11) Mears, R. J.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 8155-8156.

(12) (a) Nyzam, V.; Belaud, C. Zammattio, F.; Villiéras, J. *Bull. Soc. Chim. Fr.* **1997**, *134*, 583-592; (b) Nyzam, V. Ph. D. Thesis, Université de Nantes, France, **1996**.

(13) Chataigner, I.; Lebreton, J.; Zammattio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719-3722.

(14) Herold, T.; Schrott, U.; Hoffmann, R. W.; Schnelle, G.; Ladner, W.; Steinbach, K. *Chem. Ber.* **1981**, *114*, 359-374.

(15) Herold, T.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 768-769.

(16) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093; (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404; (c) Hertweck, C.; Boland, W. *J. Prakt. Chem.* **1999**, *341*, 83-87.

(17) Corey, E. J.; Yu, C.-M., Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.

(18) For a discussion of this effect, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224-232.

(19) (a) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs. Ann. Chem.* **1985**, 2246-2260; (b) Hoffmann, R. W.; Metternich, R. *Liebigs. Ann. Chem.* **1985**, 2390-2402.

(20) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 4239-4254.

(21) Alcohols **28f-h** were prepared according to: Yang, D.; Xu, M.; Bian, M.-Y. *Org. Lett.* **2001**, *3*, 111-114. See also: (a) Ort, O. *Org. Synth.* **1987**, *65*, 203-213; (b) Potin, D.; Dumas, F. *Synth. Commun.* **1990**, *20*, 2805-2813

(22) Ndibwami, A.; Lamothe, S.; Guay, D.; Plante, R.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 695-713.

(23) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909; (b) Ohkata, K.; Miyamoto, K.; Matsumura, S.; Akiba, K.-y *Tetrahedron Lett.* **1993**, *34*, 6575-6578; (c) Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785-1788.

(24) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112-8114.

(25) D'Oca, M. G. M.; Pilli, R. A.; Pardini, V. L. Curi, D.; Comninos, F. C. M. *J. Braz. Chem. Soc.* **2001**, *12*, 507-513.

(26) See also: (a) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500-503; (b) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293-2304.

(27) (a) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250-3263; (b) Singh, R. P.; Matteson, D. S. *J. Org. Chem.* **2000**, *65*, 6650-6653.

(28) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631-632.

(29) Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137-141.

(30) Electrophile **32b** prepared in a similar procedure as reported in reference 28. See also: Brown, H. C.; Roy, C. D.; Soundararajan, R. *Tetrahedron Lett.* **1997**, *38*, 765-768.

(31) Fardella, G.; Barbetti, P.; Grandolini, G.; Chiappini, I.; Ambrogi, V.; Scarcia, V.; Candiani, A. F. *Eur. J. Med. Chem.* **1999**, *34*, 515-523; (b) Lee, K.-H.; Huang, B.-R.; Tzeng, C.-C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 241-244; (c) Lawrence, N. J.; McGown, A. T.; Nduka, J.; Hadfield, J. A.; Pritchard, R. G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 429-431.

(32) Matsuda, H.; Shimoda, H.; Uemura, T.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2647-2652.

(33) (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94-110; (b) Janecki, T.; Blaszczyk, E.; Studzian, K.; Rózalski, M.; Krajewska, U.; Janecka, A. *J. Med. Chem.* **2002**, *45*, 1142-1145.

(34) For reviews, see Grieco, P. *Synthesis* **1975**, 67-82. See also reference 33a.

(35) For recent preparations, see: (a) Knochel, P.; Sidduri, A. R. *J. Am. Chem. Soc.* **1992**, *114*, 7579-7581; (b) Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209-3246; (c) Paquette, L. A., Méndez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301-4304; (d) Xu, M.-H., Wang, W.; Xia, L.-J., Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953-3962; (e) Dumeunier, R.; Leclercq, C.; Markó, I. E. *Tetrahedron Lett.* **2002**, *43*, 2307-2311; (f) Kang, S.-K.; Kim, K.- J.; Hong, Y.-T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1584-1586.

(36) Matsuda, F.; Ohsaki, M.; Yamada, K.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2123-2131.

(37) (a) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216-5217; (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448-3467.

(38) For some examples of products containing 3 or more contiguous stereogenic centers, see: (a) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *Perkin Trans. 1* **1998**, 9-39; (b) Yoda, H.; Katoh, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 7661-7665; (c) López-Alvarado, P.; García-Granda, S.; Álvarez-Rúa, C.; Avendaño, C. *Eur. J. Org. Chem.* **2002**, 1702-1707; (c) Harrowven, D. C.; Luca, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 4443-4444; (d) Cassayre, J.; Zard, S. Z. *J. Organomet. Chem.* **2001**, *624*, 316-326; (e)

Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999-15016.

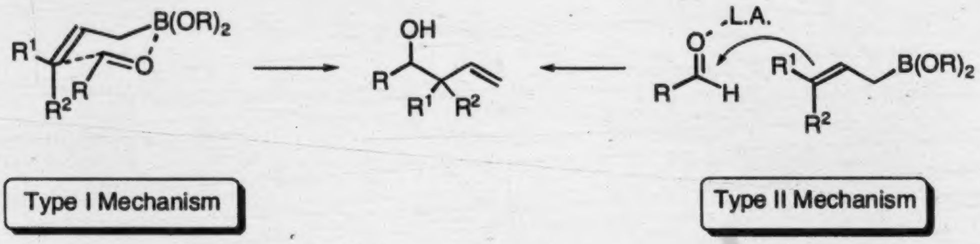
(39) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett*. **1994**, *35*, 375-375.

Chapter 4

Lewis Acid Catalysed Allylborations

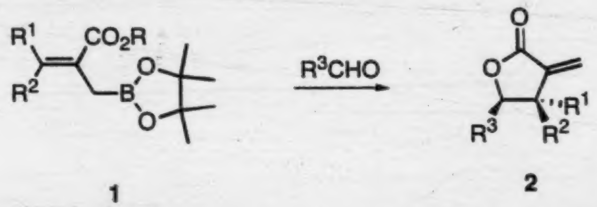
4.1 Introduction

The next major advance in this project was the discovery that an allylboration reaction can be catalysed by external Lewis acids. Prior to our research, the catalysed allylboration reaction was virtually unknown. Allylboronates are self-activating Type I reagents, where the allylation reaction is initiated by internal coordination of the aldehyde to the boron atom (Scheme 4-1). Because of this internal activation, there would appear to be no need for an external promoter. Furthermore, an external Lewis acid might compete with the boron atom for the aldehyde, leading to a switch from the highly diastereoselective Type I mechanism to the less selective, open chain Type II mechanism.



Scheme 4-1

However, we were inspired to investigate the possibility of accelerating the allylboration by the long reaction times observed with our tetrasubstituted allylboronates **1** (Scheme 4-2). As described in Chapter 3, these reagents react smoothly with aldehydes to generate diastereomerically and enantiomerically pure quaternary carbon centres. However, these allylations required extended reaction times (usually 2 weeks) or high temperatures to achieve completion. Furthermore, reaction of aliphatic aldehydes at high temperatures sometimes led to a decrease in the stereochemical purity of the product. Consequently, despite the potential utility of these reagents, there was obviously room for improvement. In addition to decreasing the reaction times, establishing a catalytic allylboration reaction would then open the door to enantioselective catalysis, where enantiomerically pure quaternary carbon centres could be generated with a substoichiometric chiral director rather than with the two, stoichiometric auxiliaries currently required.



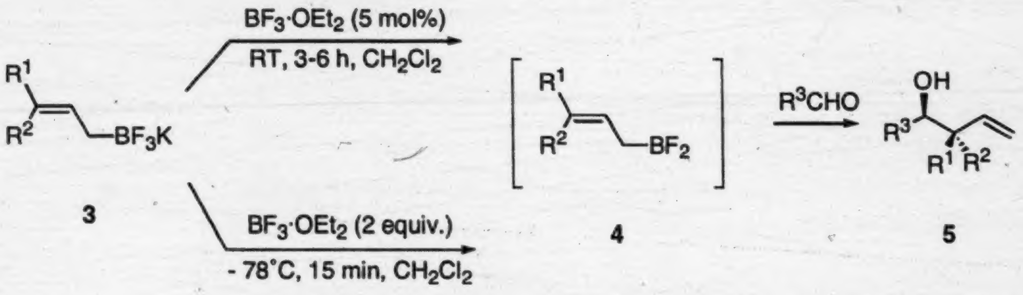
Advantages: - Generation of stereodefined quaternary carbon centre.
- Operationally simple reaction.

Disadvantages: - Excessively slow reaction.
- Two auxiliaries needed for high enantioselectivity.

Scheme 4-2

4.2 Previous Catalysed Allylborations

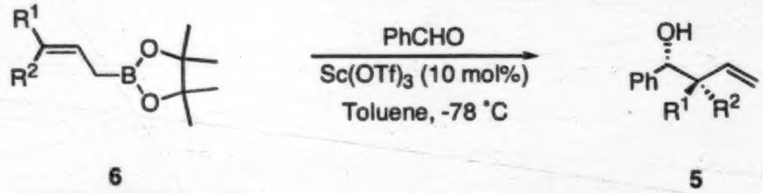
The first, formal example of a Lewis acid catalysed allylboration was reported in 1999 by Batey and co-workers.[1-3] These researchers found that trifluoroborate salts **3** undergo Type I allylation with aldehydes in the presence of catalytic amounts of $BF_3 \cdot OEt_2$ (Scheme 4-3). However, the reaction is much more efficient if two equivalents of the Lewis acid are used, and generally the reaction is run under these stoichiometric conditions. The reaction is thought to proceed via the putative difluoroborane **4**, which is produced by electrophilic removal of fluoride ion from the salt **3**.



Scheme 4-3

After publication of our initial results, Ishiyama and co-workers independently described the use of Lewis acids to catalyse the addition of simply allyl and crotylboronates

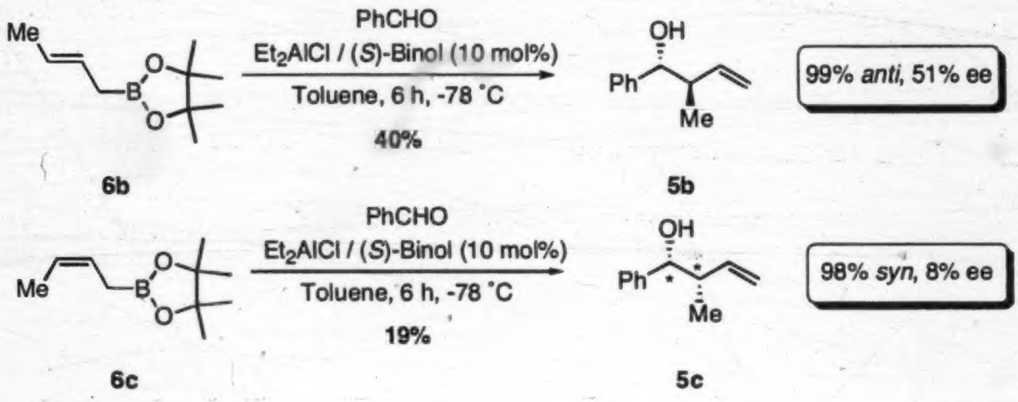
6 to aldehydes (Table 4-1).[4] This work confirmed our observation that these catalysed allylborations proceeded with the diastereospecificity seen in the uncatalysed reactions.



Entry	Boronate	Product	R^1	R^2	Yield (%)	dr (%)
1	**6a**	**5a**	H	H	80	-
2	**6b**	**5b**	Me	H	94	98
3	**6c**	**5c**	H	Me	89	98

Table 4-1. Simple catalysed allyl- and crotylborations with benzaldehyde.[4]

This group also reported an enantioselective addition using a substoichiometric amount of chiral catalyst (Scheme 4-4).[4] Although the selectivities and yields were low, this report was the first ever of an enantioselective catalysed allylboration. Due to the low selectivity of the *Z*-boronate **6c** in the reaction, the stereochemistry of the major enantiomer formed from this boronate was not determined.



Scheme 4-4

4.3 Our Proposal

We were encouraged to investigate the catalysis of allylborations by the desire to increase the rate of reaction of our γ-disubstituted allylboronates. Consideration of the transition state for the reaction gave an indication as to how to achieve this goal. Figure 4-1 shows the putative transition state for the reaction and also points out the two main events that occur in the allylboration reaction. These events are:

(1) The formation of a coordinate bond between the boron and the carbonyl oxygen of the aldehyde.
(2) The formation of a new carbon-carbon bond.

Enhancement of either of these events would increase the overall reaction rate. However, theoretical calculations by Omoto and Fujimoto have shown that the boron-oxygen coordination is the most important factor in determining the reaction rate and that the majority of the C-C bond formation occurs after the transition state.[5] This result gave a theoretical basis for earlier observations that the rate of reaction with a given allylboronate is strongly related to the electrophilicity of the boron atom.[6]

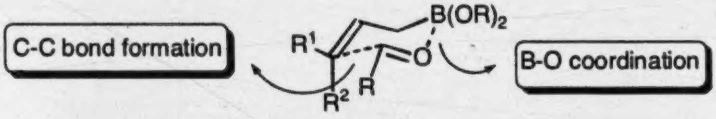


Figure 4-1. Generic transition structure for allylboration.

In light of these studies, we felt that an external Lewis acid might be able to coordinate to one of the boronate oxygens, perhaps assisted by chelation to the carboxyester (Figure 4-2). This coordination would interrupt the ability of the oxygen lone pair to delocalize into the empty p-orbital of the boron, thereby making the boron atom more electrophilic. This idea stems from an observation by Brown and co-workers that the rate of an allylboration can "be rationalized in terms of the relative availability of lone pairs of electrons on the oxygen atoms attached to boron."[6]

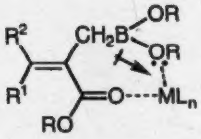


Figure 4-2. Hypothetical boronate activation by coordination of a Lewis acid

By effectively removing one of the lone pairs on the oxygens, we should render the boron more electrophilic, and strengthen the coordination of the boron to the aldehyde, which in turn would increase the overall rate of the reaction. This type of boronate activation was unprecedented prior to our work. However, we hoped that if it were possible, then perhaps it might not be limited to allylborations and could be applied to other boron mediated reactions.

Even if this electrophilic boron-activation is not possible, we believed that there were several other ways in which an external Lewis acid could catalyse reactions with our 2-carboxyester allylboronates. Reactions with these allylboronates are much slower than expected due to a reduction of the nucleophilicity of the γ-carbon caused by conjugation of the olefin to the ester. Another possible mode of catalysis is that the external Lewis acid might help to increase the nucleophilicity of the γ-carbon. The Lewis acid might achieve this increase by coordinating to the 2-carboxyester group and twisting it out of conjugation with the olefin. Although Lewis acids are generally used to increase the electrophilicity, not the nucleophilicity, of this position in conjugated carbonyl systems, we could not, *a priori*, rule out this possibility.

A third possibility is that the rate may be increased by activation of the aldehyde. Initially, we were concerned that if the aldehyde were activated solely by the external Lewis acid, the reaction might switch over to a Type II mechanism and open transition states (Figure 4-3). We wanted to avoid this scenario at all costs since we felt that this switchover might disrupt the stereospecificity observed in the thermal reaction with **1**. However, a more hopeful scenario is that the aldehyde could undergo double activation and coordinate to both the boron and the external Lewis acid. While this double-coordination would still allow for closed, Type I transition states, we considered it unlikely since double coordination has only been observed in a few, rare cases.[7]

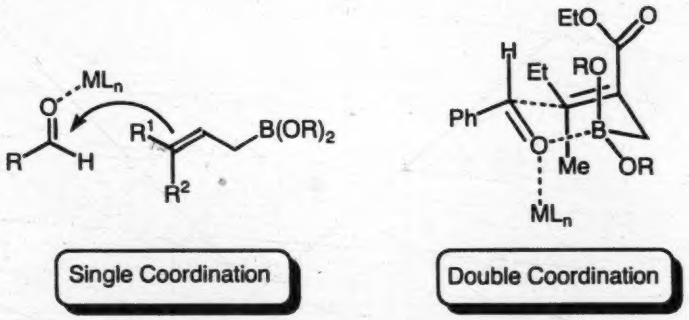


Figure 4-3. Hypothetical Lewis acid catalysis by aldehyde coordination.

One final way in which an external Lewis acid might catalyse an allylboration is through the generation of a new, more reactive allylmetal reagent (Figure 4-4). While boron is known to transmetalate with some metals (most notably with palladium in Suzuki couplings), it is not a common process. Furthermore, we would worry that even if the new allylmetal species **7** were stereospecific in its additions, the stereochemical integrity of the olefin in **1** might be lost in the transmetalation process.

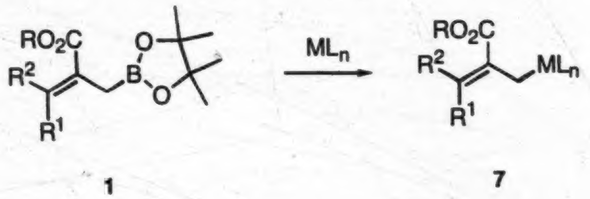


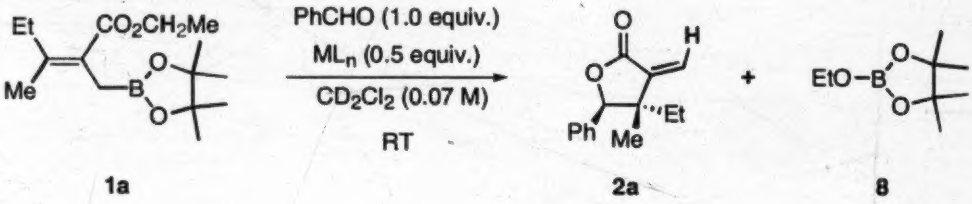
Figure 4-4. Hypothetical Lewis acid catalysis by transmetalation.

4.4 Results

4.4.1 Search for lead catalysts

The first step in our search for a catalysed allylboration was to identify possible metals that might act as catalysts. Inspired by the study of Brown and co-workers,[6] we devised a simple, NMR spectroscopy based screen. We monitored the reaction between benzaldehyde and boronate **1a** in dilute CD_2Cl_2 with 0.5 equivalents of potential catalyst (Scheme 4-5). By ^1H NMR spectroscopy, we could monitor the disappearance of the ester

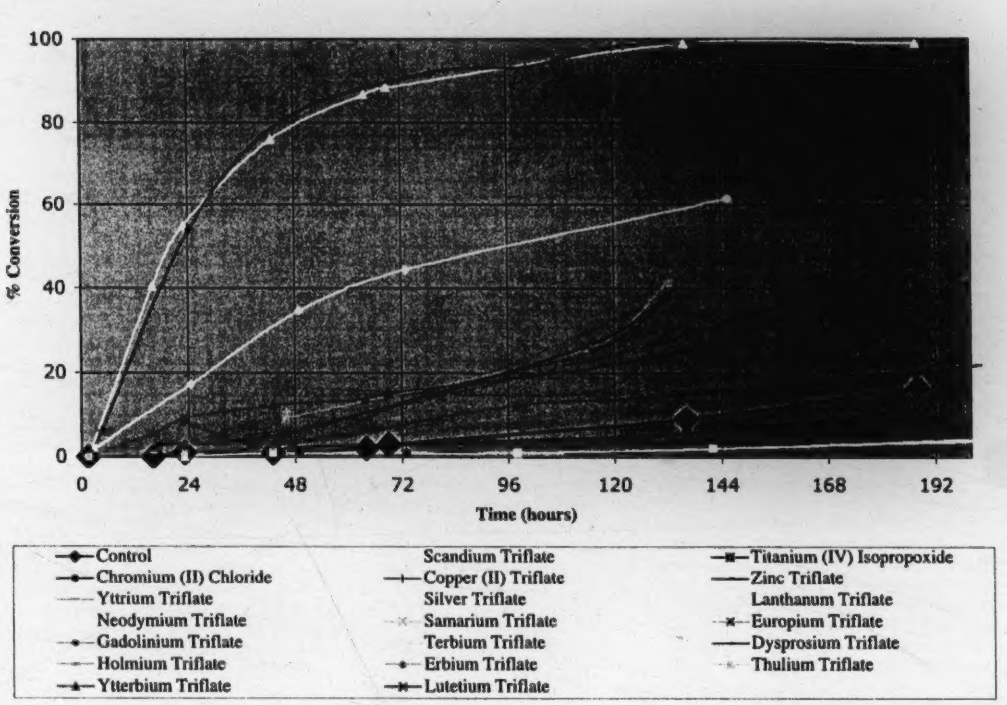
CH_2 signal from **1a** (δ 4.18 pm, quartet) and the appearance of the signal for the Z-olefin proton in **2a** (δ 6.43 ppm, singlet). All of the data presented below came from ^{1}H NMR experiments, despite the paramagnetic nature of some of the metals studied which complicated the spectra. However, we found that the ^{11}B NMR spectrum was relatively insensitive to these paramagnetic effects. In these cases, the reaction could be readily followed by ^{11}B NMR, since the boron in **1a** appears at 32 ppm, and putative by-product **8** gives rise to a signal at 23 ppm.



Scheme 4-5

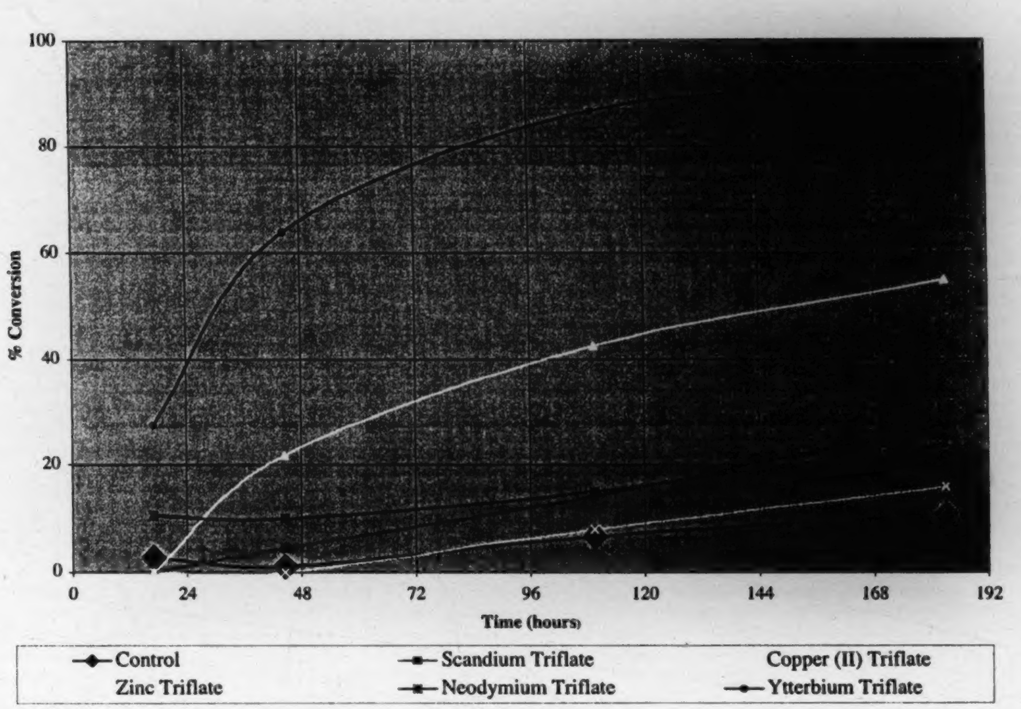
We then proceeded to scan a wide variety of transition and lanthanide metal salts. The results from this study are shown in Graph 4-1. To our surprise, a large number of metals were found to be capable of accelerating the allylboration reaction. However, two salts, scandium triflate and copper (II) triflate, displayed remarkable reactivity. In fact, reactions in the presence of these salts were over 35 times faster than the uncatalysed reaction. This large acceleration should be sufficiently high to eventually allow for effective enantioselective catalysis without significant competition from the racemic, background reaction.

Graph 4-1. Initial metal screening for allylboration catalysts. Control reaction shown with extra large diamonds.



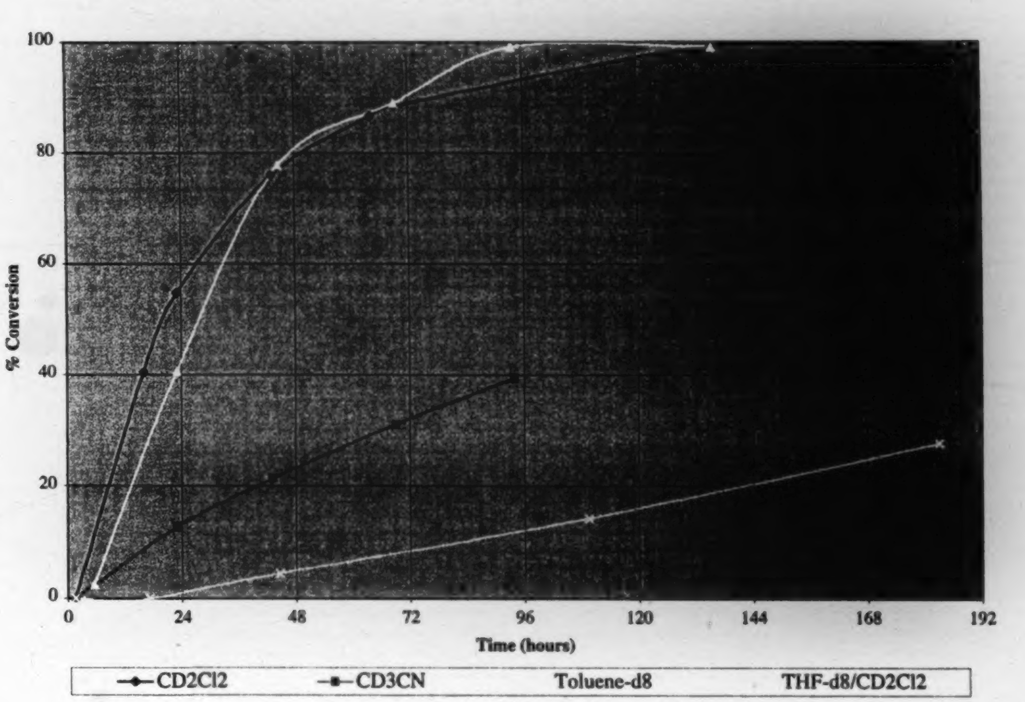
We noticed that most of the mixtures in the screen were heterogeneous, and we wondered if some of the catalysts were performing poorly due to solubility problems. Thus, we performed a second screen on a selected group of metal salts in a more polar solvent system, 1:1 THF-d_8:CD_2Cl_2 (Graph 4-2). Although many of the mixtures were still heterogeneous, we observed a marked change in reactivity in some of the catalysts. Most notably, scandium triflate, one of the best leads from the first screen, was rather inactive in this solvent mixture, while ytterbium triflate, which was moderately active in the first scan, was still a viable catalyst under these conditions.

Graph 4-2. Catalyst scan in 1:1 THF-d_8:CD_2Cl_2.



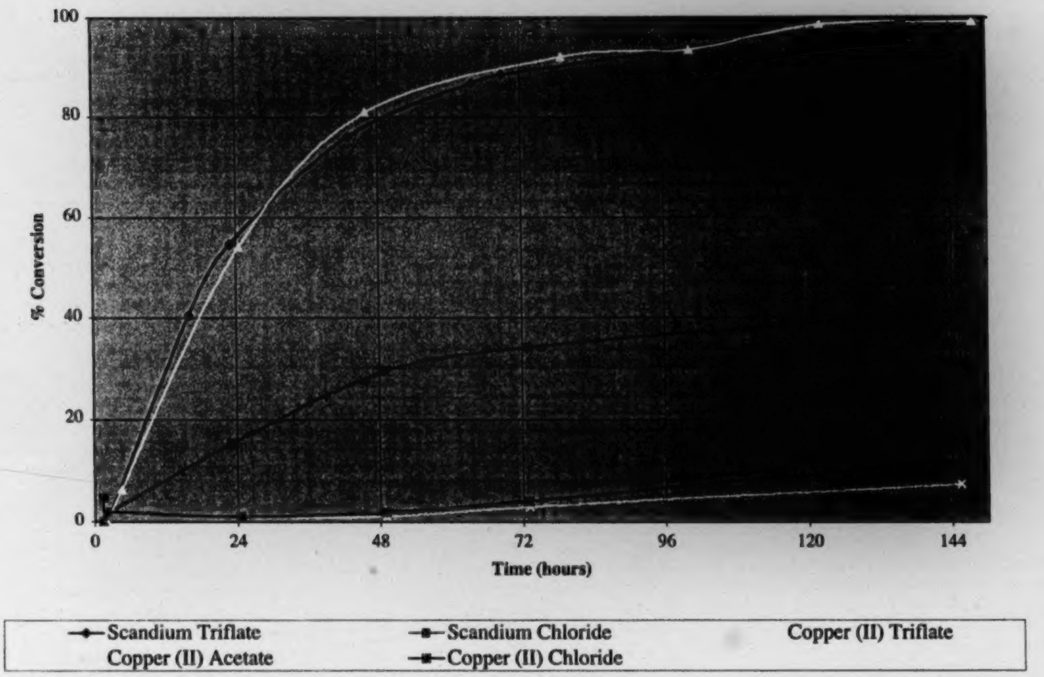
We next measured the effectiveness of one of these lead catalysts, $Sc(OTf)_3$, in various solvents (Graph 4-3). From this study we found that there was very little difference between toluene and dichloromethane as solvent, but that coordinating solvents significantly retarded the reaction.

Graph 4-3. Catalytic effectiveness of scandium triflate in various solvents.



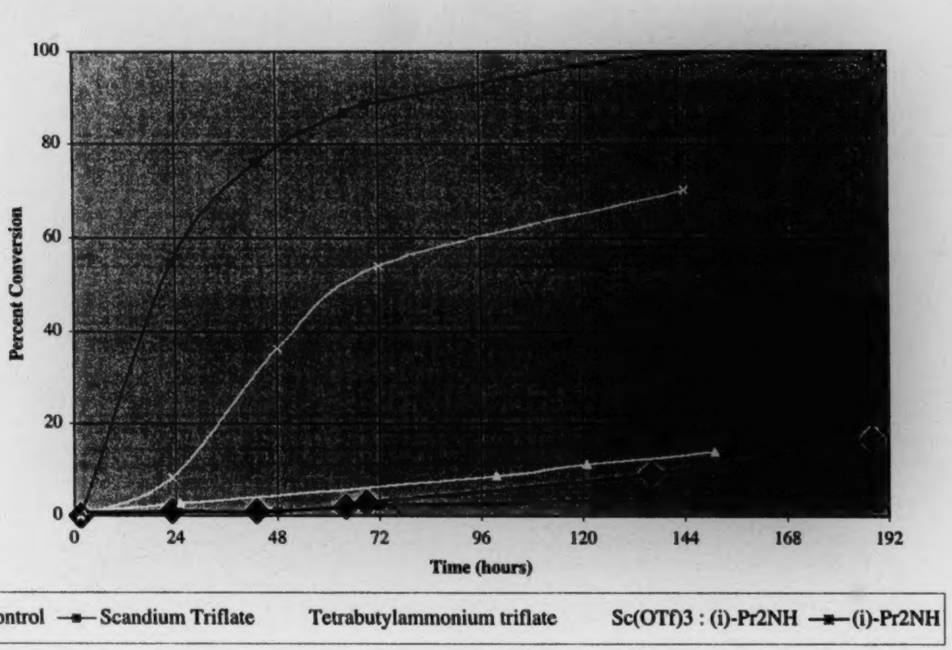
Finally, we optimized the catalytic effect versus the counter ion (Graph 4-4). From this study, we saw that the triflate salts of scandium and copper were significantly more effective than the chloride or the acetate salts.

Graph 4-4. Optimization of catalyst counter ion.



In light of these five studies, we were able to determine that scandium triflate, copper (II) triflate, and ytterbium triflate would be the best catalysts for use in a catalytic allylboration reaction. However, before proceeding to preparative scale reactions we wanted to ensure that the catalytic effect was truly due to the Lewis acidic metal. Thus, one final series of NMR scans was performed (Graph 4-5). The reaction using tetrabutylammonium triflate showed that triflate anion itself was not sufficient to cause the observed 35-fold rate enhancement. We also considered the possibility that the true catalyst might be triflic acid, generated *in situ* by adventitious water and triflate anion. The preceding reaction cast doubt on this possibility, and Kobayashi has shown that aqueous solutions of rare earth metal triflates do not generate significant amounts of triflic acid.[8] Nevertheless, we checked the ability of $Sc(OTf)_3$ to catalyse the reaction in the presence of an acid scavenger. Thus, the reaction was performed using a 1:1 mixture of $Sc(OTf)_3/(i)\text{-}Pr_2NH$. This reaction was marginally, but not significantly, slower than the reaction without amine present, showing that the Lewis acid was able to catalyse the reaction without generating triflic acid. Diisopropylamine alone was not an effective catalyst. While the difference in reaction rates between the scandium catalysed reactions in the presence and absence of diisopropylamine might be due to a sequestering of the catalyst by the amine, it might also be due to coordination of the amine to the boronate.

Graph 4-5. Allylborations in the presence of triflate anion and under acid-scavenging conditions.



4.4.2 Diastereoselective metal-catalysed allylborations

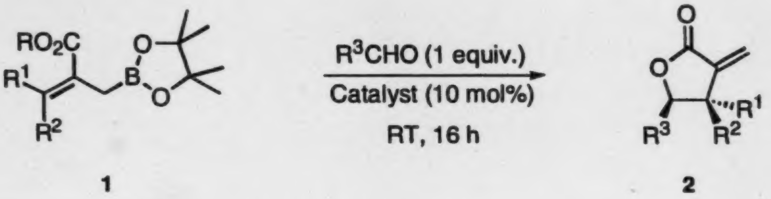
Now that we had identified three lead catalysts for our allylboration reaction, it remained to be shown that the catalytic effect would hold on a preparative scale and with truly catalytic loadings. We hoped to achieve three goals with this reaction:

(1) A reaction that was complete within a maximum of 12-16 hours at room temperature.

(2) A maximum of 10 mol% catalyst loading.

(3) Retention of the stereospecificity seen in the thermal allylboration.

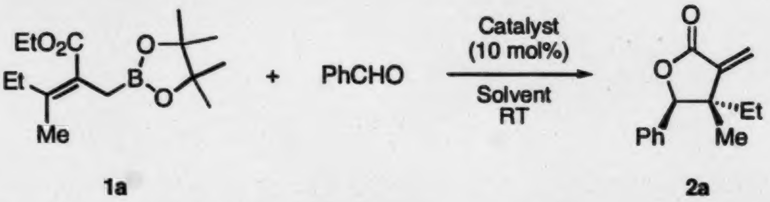
These goals are shown graphically in Scheme 4-6, and we were pleased to achieve all three of them over the course of this study.[9] We found that both aromatic and aliphatic aldehydes can be effectively allylated under these catalytic conditions. However, both kinds of aldehydes show minor differences in their reactivity, and for this reason they will be discussed separately below.



Scheme 4-6

4.4.2.1 *Catalytic allylboration with aromatic aldehydes*

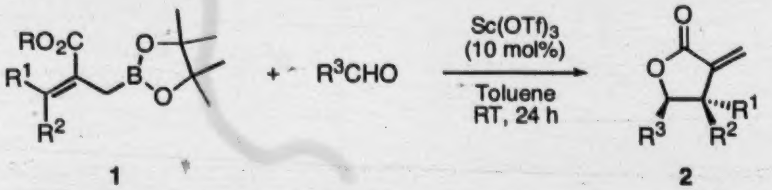
Our initial catalytic reactions with benzaldehyde showed a dramatic improvement over the thermal reactions (Table 4-2). Reactions with all three of our lead catalysts under practical conditions (10 mol% loadings, 0.5–1 M concentrations, 12-24 h) gave excellent yields of the lactone **2a**. Most importantly, the stereospecificity of the thermal reaction was preserved, and the lactones **2a** were all formed stereochemically pure. It is remarkable that these catalytic reactions show the same yields and reaction times as the uncatalysed processes, except at much lower temperatures (*c.f.*, entry 8).



Entry	Catalyst	Reaction Conditions	Reaction time	Yield (%)
1	$Sc(OTf)_3$	0.5 M in toluene	20 h	71
2	$Sc(OTf)_3$	1 M in toluene	24 h	93
3	$Sc(OTf)_3$	1 M in CH_2Cl_2	24 h	78
4	$Cu(OTf)_2$	0.5 M in toluene	20 h	67
5	$Cu(OTf)_2$	1 M in toluene	16 h	73
6	$Yb(OTf)_3$	0.5 M in toluene	20 h	91
7	$Yb(OTf)_3$	1 M in CH_2Cl_2	16 h	93
8	None	Toluene, 80 °C	16 h	60

Table 4-2. Lewis acid catalysed allylborations with benzaldehyde and boronate **1a**.

This remarkable catalytic effect was extended to the reaction of other allylboronates with electron poor or neutral aldehydes (Table 4-3). As above, all of the lactone products were isolated with a stereochemical purity reflecting that of the boronate used.



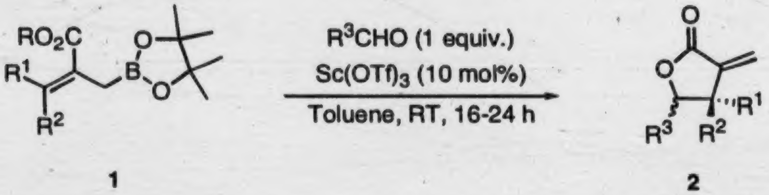
1 **2**

Entry	Boronate	Lactone	R^1	R^2	R^3	Yield (%)
1[b]	**1a**	**2b**	Et	Me	4-AcO-C_6H_4-	57
2[a]	**1b**	**2c**	Me	Bu	2-I-C_6H_4-	48
3[a]	**1b**	**2d**	Me	Bu	C_6F_5-	47
4[b]	**1b**	**2e**	Me	Bu	4-NO_2-C_6H_4-	58
5[b]	**1b**	**2f**	Me	Bu	1-Naphthyl	44
6[a]	**1b**	**2g**	Me	Bu	4-Me-C_6H_4-	75
7	**1c**	**2h**	Me	Me	4-Br-C_6H_4-	62

Table 4-3. Catalytic allylborations with aromatic aldehydes. All boronates and lactones were >20 : 1 dr. R = Et or Me. [a] 1.5 equiv. aldehyde used. [b] 1 equiv. of aldehyde used.

A major difference was observed in the water tolerance of scandium triflate and copper triflate as catalysts. Copper triflate lost all catalytic ability in the presence of 1 equivalent of added water, but catalysis could be restored to these reactions by adding molecular sieves. However, reactions with scandium triflate retained their catalytic effect in the presence of up to one equivalent of added water, but showed no catalysis at all in the presence of molecular sieves. The reasons why sieves shut down catalysis with scandium are not clear at the moment.

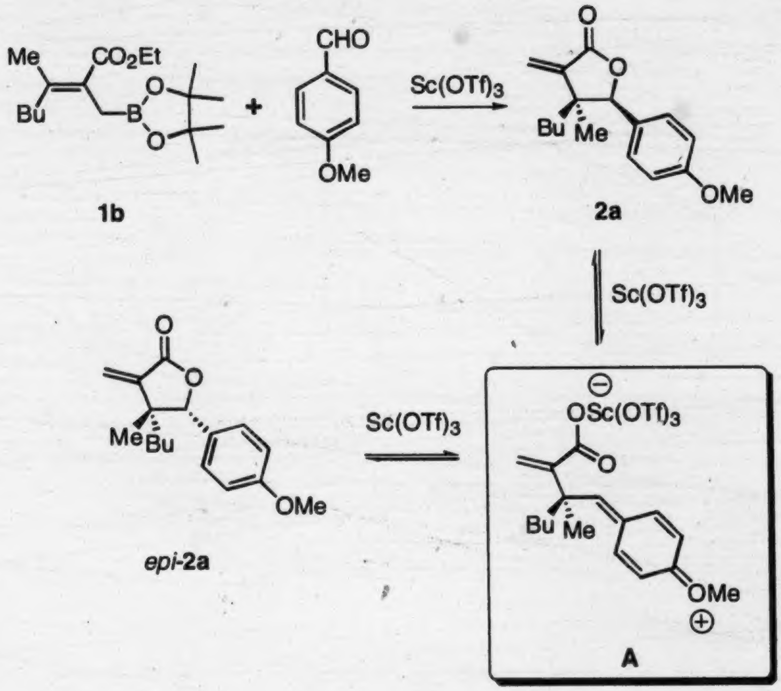
One major limitation to this catalytic manifold is that certain aldehydes do not give stereochemically pure products (Table 4-4). To date, this problem has only been observed with electron rich aromatic aldehydes and α,β-unsaturated aldehydes. This stereochemical disappointment is observed with all three lead catalysts, and we have yet to find conditions that allow for the effective catalytic allylation of these aldehydes. However, all of these substrates give the expected, stereochemically pure products in the uncatalysed, thermal reaction (see Chapter 3).



Entry	Lactone	R^1	R^2	R^3	Yield (%)	dr of **2**
1[b]	**2i**	Et	Me	2-MeO-C_6H_4-	66	2 : 1
2	**2j**	Et	Me	*E*-2-C_6H_5-1-ethenyl	ND	1.5 : 1
3	**2k**	Et	Me	*E*-2-(4-NO_2-C_6H_4)-1-ethenyl	ND	2.8 : 1[e]
4[a]	**2l**	Me	Bu	4-MeO-C_6H_4-	39	1.8:1
5[a]	**2m**	Me	Bu	*E*-1-propenyl	61	1:1
6	**2n**	Et	Bu	2-Furyl-	45	2.5 : 1[c]
7[d]	**2o**	Et	Bu	4-MeS-C_6H_4	69	2.5 : 1

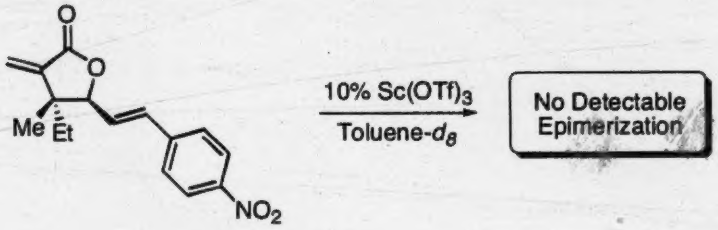
Table 4-4. Catalysed allylborations with problematic aldehydes. All boronates **1** were >20:1 dr except as noted. ND = yield not determined. R = Me or Et. [a] 1.5 equivalents of aldehyde used. [b] Initial boronate was of 10:1 dr. [c] Thermal reaction gave the product as one isomer in 74% yield. [d] Reaction run for 7 days. [e] Thermal reaction gave the product as one isomer in 80% yield.

We believe that this stereochemical mixture arises from epimerization of the product lactones **2**, perhaps via an ionization process aided by the catalyst as depicted below (Scheme 4-7). To date, this problem has only been observed with aldehydes bearing groups that could stabilize the putative carbocation shown in the proposed Intermediate **A**. We do not believe that the stereochemical mixture derives from a competing Zimmerman-Traxler transition state because this problem has not been observed with sterically less demanding aldehydes (butanal) nor with aldehydes that could possibly coordinate to the catalyst (benzyloxyacetaldehyde or 4-acetoxybenzaldehyde).



Scheme 4-7

We sought to gain evidence for this hypothesis by attempting to induce epimerization of stereochemically pure lactone **2k** with scandium triflate (Scheme 4-8). However, no epimerization of the lactone could be detected by ^{1}H NMR spectroscopy, even after several days in dilute solution and overnight in concentrated solution.

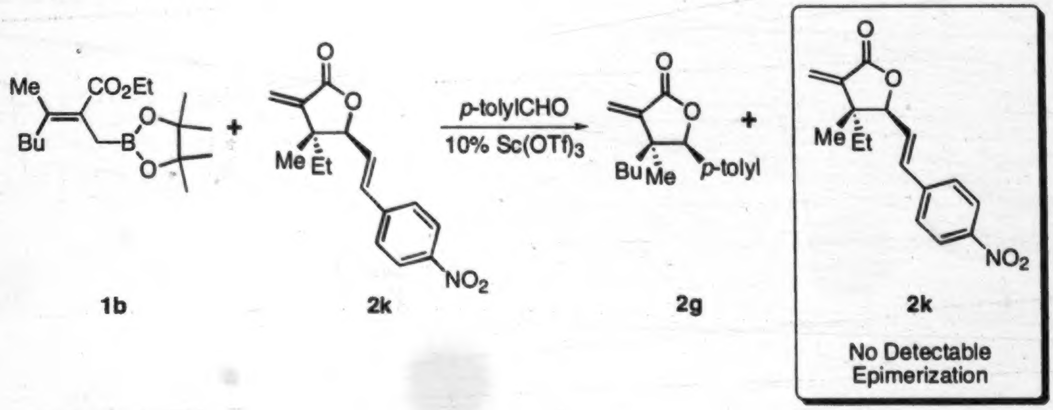


2j

Scheme 4-8

This result does not rule out the hypothesis outlined in Scheme 4-7, but it does show that the Lewis acid alone is not capable of promoting this epimerization process. Perhaps the Lewis acid, in conjunction with another species (possibly the borate or the pinacol liberated by the allylboration) is causing the epimerization.

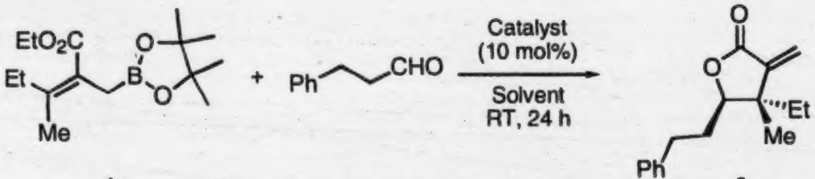
One test of this theory is to perform the allylboration of an aldehyde (*e.g.*, between **1b** and *p*-tolualdehyde) in the presence of a completely unrelated, stereochemically pure lactone (*e.g.*, **2k,** Scheme 4-9) and then determine whether **2k** underwent any epimerization. This experiment would subject **2k** to the same reaction conditions that it would be under following its own preparation. If the lactone **2k** remained stereochemically pure after this test, then it would truly rule out any post-reaction epimerization. This control reaction would also be able to exclude any possible, albeit extremely unlikely, retro-allylboration and cross-over mechanisms. In the event, both lactones **2g** and **2k** were present in the reaction mixture in stereochemically pure form, effectively excluding a post-lactonization epimerization process.



Scheme 4-9

4.4.2.2 *Catalytic allylboration with aliphatic aldehydes*

We next wanted to extend this catalytic manifold to the allylboration of aliphatic aldehydes. Using hydrocinnamaldehyde as a model substrate we performed a brief solvent and catalyst scan using slightly different conditions than those described for aromatic aldehydes (Table 4-5). Like reactions with aromatic aldehydes, these reactions were stereospecific and complete in reasonable time frames at room temperature. From these results we saw that all three lead catalysts gave effective allylation in toluene, but that scandium triflate was clearly the best catalyst in dichloromethane. However, catalysed allylborations in CH_2Cl_2 often went dry over the course of the reaction, most likely due to the high volatility of this solvent. Consequently, we chose scandium triflate in toluene for our general allylboration conditions.

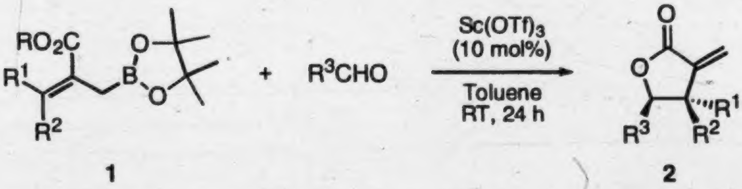


1a **9a**

Entry	Catalyst	Solvent	Yield (%)
1	$Sc(OTf)_3$	Toluene	64
2	$Cu(OTf)_2$	Toluene	63
3	$Yb(OTf)_3$	Toluene	66
4	$Sc(OTf)_3$	CH_2Cl_2	62
5	$Cu(OTf)_2$	CH_2Cl_2	52
6	$Yb(OTf)_3$	CH_2Cl_2	38

Table 4-5. Solvent and catalyst scan for catalytic allylboration of aliphatic aldehydes with **1a**. Reaction performed with 1.5 equivalents of aldehyde and 0.5 M concentration.

Under these established conditions a wide variety of aldehydes could be effectively allylated (Table 4-6). While the catalysed reaction of aromatic aldehydes showed a marked improvement over the thermal reaction, the improvement seen in reaction with aliphatic aldehydes was even more dramatic. As above, the reaction times were much shorter at lower temperatures and the stereospecificity of the thermal reaction was preserved. Furthermore, since these reactions are run at temperatures well below 110°C, the stereochemical erosion sometimes observed with aliphatic aldehydes in the thermal reactions is completely suppressed here.

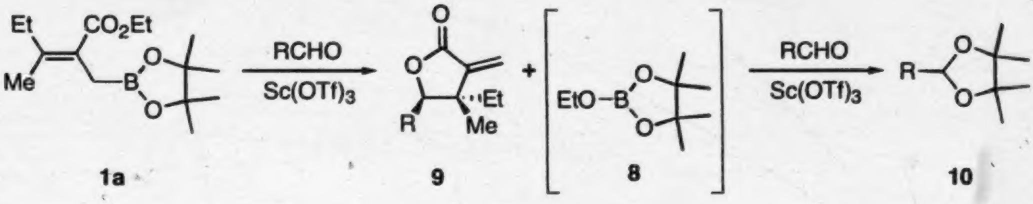


Entry	Boronate	R^1	R^2	R^3	Lactone	dr	Yield (%)
1	**1a**	Et	Me	$BnOCH_2$	**9b**	19:1	53
2	**1a**	Et	Me	(*i*)-Bu	**9c**	>20:1	46[a]
3[b]	**1a**	Et	Me	(*c*)-Hex	**9d**	10:1[c]	54
4	**1b**	Me	Bu	(*c*)-Hex	**9e**	>20:1	32
5	**1b**	Me	Bu	(*i*)-Pr	**9f**	>20:1	32
6	**1b**	Me	Bu	(*i*)-Bu	**9g**	>20:1	61
7	**1b**	Me	Bu	Bu	**9h**	>20:1	62
8	**1d**	H	Me	$BnOCH_2$	**9i**	>20:1	33[a]

Table 4-6. Catalysed allylborations with aliphatic aldehydes. 1.5 equiv. of aldehyde used. R = Me or Et. [a] 1 equivalent of aldehyde used. [b] Reaction performed using $Cu(OTf)_2$ as catalyst. [c] Boronate of 12:1 dr used in the reaction.

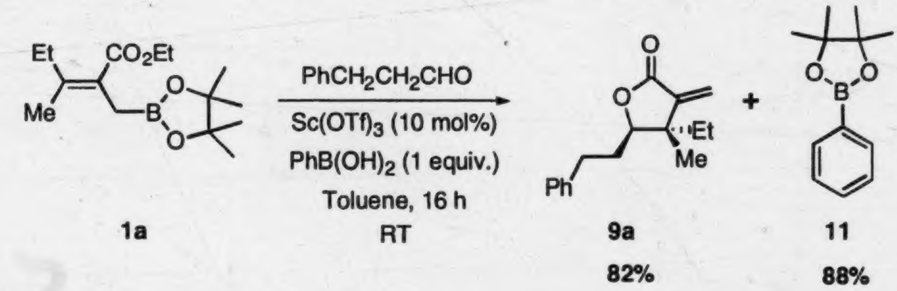
The most dramatic improvement in using this catalytic manifold is that we were now able to obtain allylation products from hindered aldehydes (entry 3-5), substrates which previously failed to give effective thermal reactions. Although room temperature reactions with these hindered substrates were sluggish, gentle heating allowed for reactions to reach completion within 16 h. Also, it appears that copper triflate is a better catalyst for these reactions than scandium triflate (entries 3 and 4). The low yield observed with isobutyraldehyde (entry 5) is probably due to the volatility of the aldehyde.

Unlike the relatively straightforward reactions with aromatic aldehydes, the initial catalytic reactions with aliphatic aldehydes were plagued by low yields of lactone **9** and the competition of several side-reactions. Consequently, significant optimizations were required. First, the reactions with aliphatic aldehydes were run at a concentration of 0.5 M in order to avoid self-condensation of the aldehyde. While reactions run at 1 M concentrations only showed trace amounts of self-condensation, this side reaction was completely suppressed under the more dilute conditions. More importantly, however, is that an excess of the aldehyde is required in order to obtain acceptable yields. This excess is required because of the formation of significant amounts of the acetal **10** from unreacted aldehyde and pinacol, liberated after the allylboration (Scheme 4-10). The observation of acetal byproduct was quite surprising because it was completely absent in the reactions with aromatic aldehydes, although Lewis acids are known to catalyse acetal formation.[10,11]



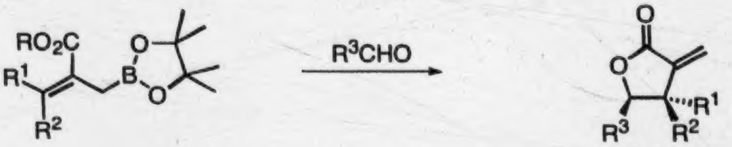
Scheme 4-10

While we can compensate for this side reaction by adding excess aldehyde, a much better solution would be to find conditions to completely suppress it. Not only is the use of excess aldehyde wasteful (especially with precious aldehydes), in many cases the acetal is difficult to remove from the lactone product. Fortunately, we have found a remedy for this problem that allows the equimolar catalytic reaction with aliphatic aldehydes. This remedy is the addition of a stoichiometric amount of phenylboronic acid to the mixture to act as a pinacol scavenger (Scheme 4-11). Under these conditions, acetal formation is almost completely suppressed and reasonable yields of lactone products are available from only one equivalent of aldehyde. In all cases studied to date, the phenylboronic pinacolate **11** is easily removed from the lactone products by flash chromatography.



Scheme 4-11

A comparison of the various methods for allylborating aliphatic aldehydes is shown in Table 4-7. From this table, it is clear that this second generation method using $Sc(OTf)_3$ catalysis with $PhB(OH)_2$ scavenging (entries 1, 3, and 6) is superior to either the thermal reaction (entry 5) or the first generation method of scandium catalysis without $PhB(OH)_2$ (entries 2, 4 and 7).



1a: R^1= Et, R^2= Me
1d: R^1= H, R^2= Me

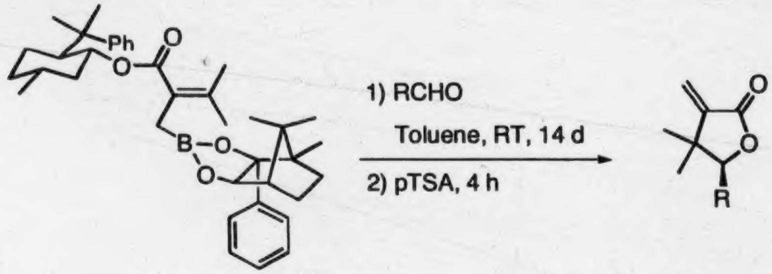
9b: R^1= Et, R^2= Me, R^3= $BnOCH_2$
9c: R^1= Et, R^2= Me, R^3= (*i*)-Bu
9i: R^1= H, R^2= Me, R^3= $BnOCH_2$

Entry	Boronate	Lactone	Equivalents of R^3CHO	Conditions[a]	Yield of **9** (%)	dr of **9**
3	**1a**	**9b**	1.0	Second Generation	54	>20:1
4	**1a**	**9b**	1.5	First Generation	53	>20:1
5	**1a**	**9b**	1.5	Thermal	33	9.5:1[b]
6	**1a**	**9c**	1.0	Second Generation	66	>20:1
7	**1a**	**9c**	1.0	First Generation	46	>20:1
1	**1d**	**9i**	1.0	Second Generation	66	>20:1
2	**1d**	**9i**	1.0	First Generation	33	>20:1

Table 4-7. Comparison of methods for the allylboration of aliphatic aldehydes with **1**. R = Me or Et. [a] Conditions used: Second Generation: $Sc(OTf)_3$ (10 mol%) with $PhB(OH)_2$ (1 equivalent); First Generation: $Sc(OTf)_3$ (10 mol%); Thermal: refluxing toluene. [b] Initial boronate was >20:1 pure.

4.4.3 Enantioselective catalysed allylborations

The next step in this project is to achieve a catalytic, enantioselective allylboration reaction. Currently there are no effective methods for controlling the absolute stereochemistry of an allylboration with a substoichiometric chiral auxiliary; in fact, with one exception, there are none reported at all.[4] Not only would this achievement be an important advance for allylboration chemistry, in the context of our research, it would present one of the first, general, catalytic preparations for enantiopure quaternary carbon centres. As described in Chapter 3, these quaternary centres are available from the reaction of a tetrasubstituted allylboronate **12** which bears two chiral auxiliaries (Scheme 4-12). While this reaction is highly selective, it leaves much to be desired in terms of efficiency. Firstly, both of the auxiliaries required for effective allylation with **12** must be installed separately. Secondly, the reaction is quite slow, and requires 2 weeks to reach completion. Obviously, a catalytic approach would be a welcome improvement to this methodology.

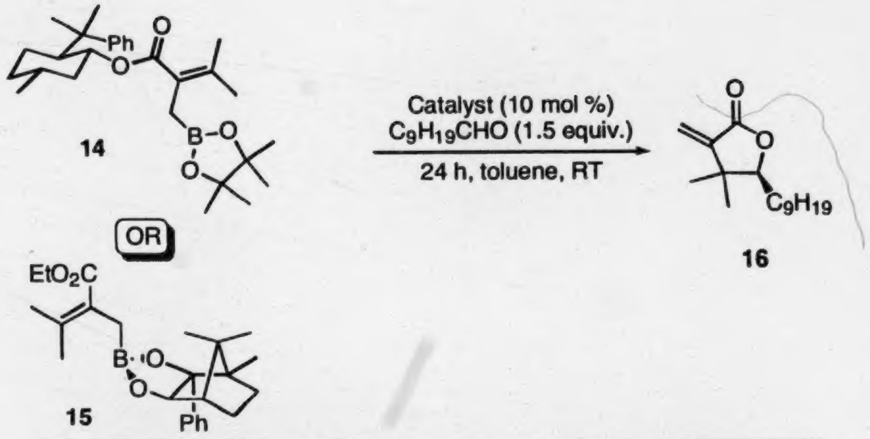


12

13, ee >95%

Scheme 4-12

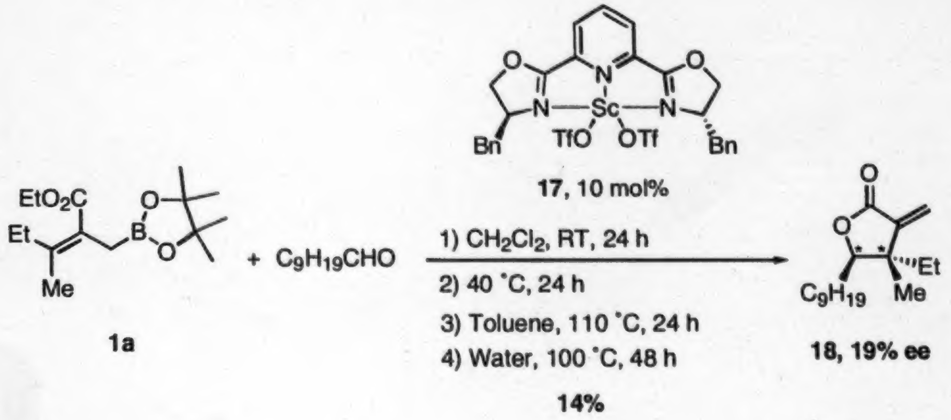
Our first attempt to increase the efficiency of our enantioselective preparation of quaternary carbon centres was to apply the new catalytic manifold to the reaction of an allylboronate bearing only one auxiliary (Table 4-8). Although the use of a stoichiometric rather than a sub-stoichiometric chiral auxiliary is not our ultimate goal, the use of a single auxiliary would already be an improvement over the existing protocols. However, these reactions were not successful, and generally gave lower yields and selectivities than obtained under the thermal conditions. It was often found that the enantiomer produced in the catalysed reaction was the opposite to that generated in the thermal reaction. These results clearly show that the Lewis acid is disrupting the transition state of the reaction.



Entry	Boronate	Catalyst	Yield (%)	ee (Enantiomer)
1	**14**	$Sc(OTf)_3$	29	10% (*R*)
2	**14**	$Cu(OTf)_2$	93	71% (*S*)
3	**14**	$Yb(OTf)_3$	30	31% (*S*)
4	**15**	$Sc(OTf)_3$	53	3% (*R*)
5	**15**	$Cu(OTf)_2$	31	13% (*R*)
6	**15**	$Yb(OTf)_3$	37	21% (*R*)

Table 4-8. Catalysed enantioselective allylborations. Non-catalysed reaction with the β-naphthyl analogue of **14** gave 82% ee for the (*S*)-enantiomer; non-catalysed reaction with **15** gave 51% ee for the (*S*)-enantiomer. See Chapter 3 for details.

A loftier goal of ours is to obtain highly selective reactions using substoichiometric amounts of the chiral auxiliary – true enantioselective catalysis. Unfortunately, we have yet to find an effective and selective catalytic system for our system. So far, we have only investigated a few enantioselective systems for scandium, and all show very low catalytic activity. Specifically, reactions with Kobayashi's binol-amine system,[12] as well as Evans' PyBOX-scandium system (both as the hexafluoroantimonate complex[13] and as the triflate complex **17**[14]) gave no appreciable product formation after 24 hours. In this latter attempt (Scheme 4-13), forcing conditions eventually led to the formation of the product **18** in low yield and poor selectivity. The absolute stereochemistry of lactone **18** has not been assigned.



Scheme 4-13

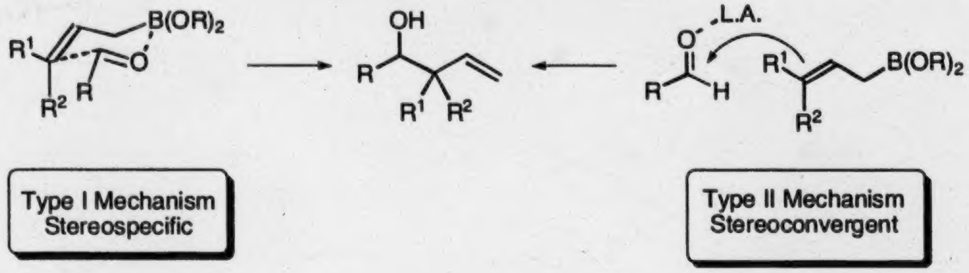
The general problem with these reactions is that the chiral ligands used close down the catalytic effect. One common feature of all three systems is the use of amine-based auxiliaries. Although the catalytic reaction is slowed in the presence of amines (see Graph 4-5, page 114), there is no reason *a priori* to believe that the presence of nitrogen containing ligands is the problem. The next step in this project would be to screen these catalytic systems with metals other than scandium. Recalling that ytterbium triflate gave a significantly better rate of reaction in THF than scandium triflate (Graph 4-2, page 111), one would not be surprised to find a metal that would offer better results in these enantioselective additions.

4.4.4 Mechanism of the metal-catalysed allylboration

Now that we had established practical conditions for the Lewis acid catalysed allylboration reaction, we turned our attention to determining the mechanism by which these additions proceed. Besides satisfying the usual academic curiosity, a better understanding of the mechanism would allow for a rational and more effective approach to further optimization of the reaction, especially in the enantioselective catalysed reactions. Although these mechanistic studies are still in their infancy, the data presented below present the case for a closed, cyclic transition state featuring a Lewis acid-boronate complex. Furthermore, we believe that the rate acceleration derives from an increase in the electrophilicity of the boron, induced by this complex. While the data below support this proposal over other possibilities, the preliminary nature of these studies means that nothing can yet be consider conclusive.

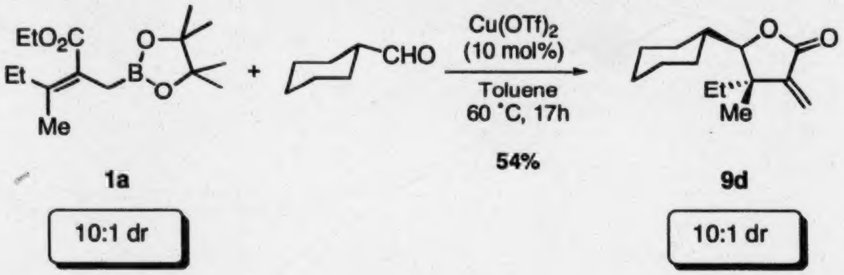
4.4.4.1 *Type I or Type II Mechanism*

The first question to address is whether the reaction proceeds via a closed, Type I mechanism or via an open, Type II mechanism (Scheme 4-14). The strongest evidence for one mechanism over the other comes from the stereochemistry of the products of the allylations. The Type I mechanism is able to transfer the stereochemistry of the allylboronate to the product, and thus the diastereoisomer of the product formed in these reactions depends on the diastereoisomer of the starting material used. In contrast, the Type II pathway tends to be stereoconvergent, and thus the same isomer of product dominates regardless of the *E/Z* stereochemistry of the starting material.



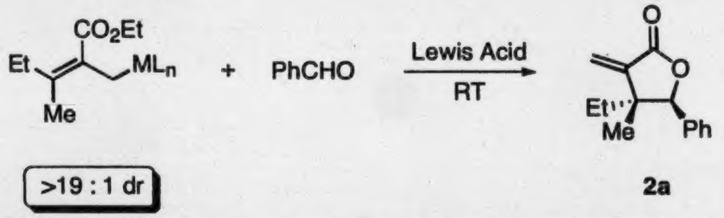
Scheme 4-14

The stereospecificity observed in the catalysed allylborations is consistent with that of the Type I mechanism. The reaction of an allylboronate of moderate stereochemical purity is especially telling (Scheme 4-15). This result confirms that the high stereochemical purity generally observed in the products of the catalysed allylboration reaction comes from a transfer of stereochemistry from stereochemically pure allylboronates and not from a stereoconvergent process that favours one isomer of the product over another. Although not impossible, it is difficult to imagine an open transition state that would allow for such a perfect transfer of stereochemistry from the allylboronate **1a** to the lactone **9d**.



Scheme 4-15

Further evidence that the catalysed allylboration is a Type I process comes from the reaction of benzaldehyde with allylstannane and allylsilane compounds **19** and **20** (Table 4-9).[15] Reactions of these known Type II reagents with benzaldehyde gave significantly different stereochemical results than the analogous allylboronate **1a**, showing that the allylboronate **1a** does not behave like a Type II reagent in the presence of an external Lewis acid.



2a

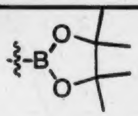
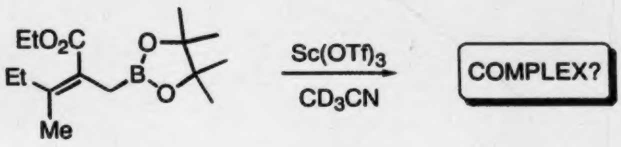
Entry	Allylmetal	ML_n	Lewis Acid	Conditions	Yield (%)	dr of **2a**
1	**1a**		$Sc(OTf)_3$ 10 mol%	Toluene 24 h	93	19:1
2	**19**	$SnBu_3$	$Sc(OTf)_3$ 50 mol%	CH_2Cl_2 24 h	21	4:1
3	**20**	$SiMe_3$	$TiCl_4$ 300 mol%	Toluene 14 d	21	3:1

Table 4-9. Comparison of allylboronate **1a** with the analogous allylstannane **19** and allylsilane **20**.

4.4.4.2 NMR Studies: Evidence for formation of a boronate:scandium complex

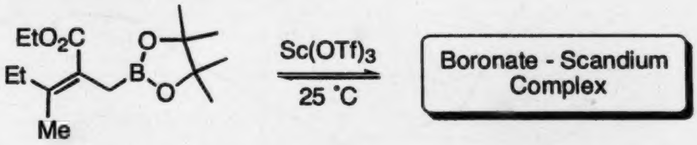
To try to understand how these Lewis acid catalysed allylborations operate, we studied the effect that varying the amount of scandium triflate present would have on the NMR spectrum of allylboronate **1a** in the absence of aldehyde (Scheme 4-16). The aim of this study was to find evidence for the formation of an activated boronate:scandium complex. The catalyst, solvent and substrate were all carefully chosen for this study. Scandium (III) is not a paramagnetic nucleus and its presence would not interfere with the spectra of other nuclei. Also, scandium is NMR active and might allow us another analytical probe. The boronate **1a** was chosen because it is unsymmetrical about the γ-carbon and acetonitrile was used because it gives homogeneous mixtures.



1a

Scheme 4-16

We were pleased to find that titration of an NMR solution of boronate **1a** with $Sc(OTf)_3$ led to a very clean spectrum showing only two species, the free boronate **1a** and the putative complexed boronate **21** (Table 4-10). Furthermore, the amount of complex formed was directly related to the amount of scandium added, with one equivalent of complex formed for every two equivalents of scandium added. At present, we cannot be sure if this 2:1 relationship reflects the stoichiometry of the complex or the position of the equilibrium between free and bound boronate.



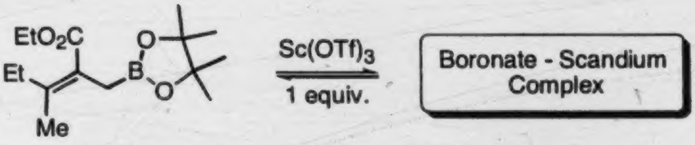
1a **21**

Entry	Equivalents of $Sc(OTf)_3$	21: **1a** Ratio
1	0.5	0.5 : 1
2	1	1.2 : 1
3	1.5	3 : 1
4	2	10 : 1

Table 4-10. Titration of a solution of boronate **1a** with $Sc(OTf)_3$.

We were not able to determine the amount of free and complexed scandium by ^{45}Sc NMR because of the poor resolution of the spectra. ^{19}F NMR spectra showed only a single, sharp peak, which suggests either the formation of a complex where all of the triflate anions are equivalent or that complexed and free triflate anions are equilibrating very rapidly.

Attempts to change the position of this equilibrium by cooling the 1:1 mixture were inconclusive (Table 4-11). Cooling the mixture from RT to – 10 °C gave a mixture where more complex was produced; however, further cooling gave a mixture with the same composition as at RT. At the moment we cannot be certain if entry 2 is a rogue result or if it suggests that the equilibrium between **21** and **1a** is more complicated than the scheme in Table 4-10 suggests.

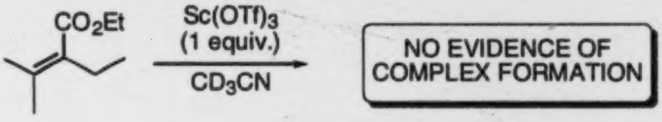


1a **21**

Entry	Temperature (°C)	Ratio of **21** : **1a**
1	25	1.2 : 1
2	-10	1.4 : 1
3	-40	1.2 : 1
4	-50	1.2 : 1

Table 4-11. Temperature dependence of the NMR composition of 1:1 mixture of boronate **1a** and $Sc(OTf)_3$.

To determine the importance of the boronic ester unit in the formation of this complex, we conducted a control experiment with **22** (Scheme 4-17). Treatment of this α,β-unsaturated ester with scandium triflate showed no evidence for the formation of a complex. The ^{1}H NMR spectrum of **22** was virtually unchanged even after the addition of one full equivalent of scandium triflate. This result shows that the boronic ester is essential for complex formation and lends credence to our boronate-activation hypothesis.



22

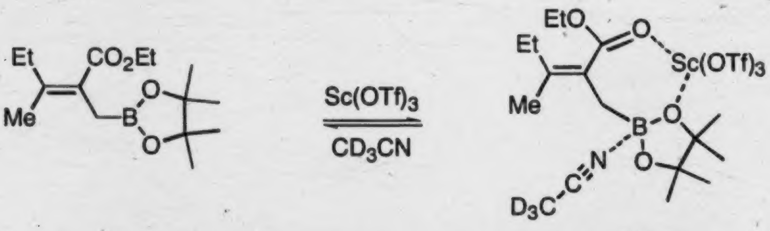
Scheme 4-17

4.4.4.3 NMR Studies: Insights into the origin of the catalytic effect

All of the evidence obtained thus far suggests that the catalysed allylboration reaction proceeded via a closed, cyclic transition state following formation of a scandium-allylboronate complex. However, there were still several questions that needed to be answered, such as: where does the scandium bind to **1a** in the transition state and how does this binding incite the catalytic effect? Section 4.3 outlined five possible ways that a Lewis acid might catalyse an allylboration. Of these ways, the stereospecificity observed with the reaction already excludes the simple coordination of the aldehyde to the Lewis acid as a possibility. However, these simple stereochemical arguments do not distinguish between the other four possibilities. To evaluate these possibilities, we studied a 1:1 mixture of boronate **1a** and scandium triflate in CD_3CN. The results of this study as they pertain to the different hypothetical modes of catalysis are presented below.

4.4.4.3.1 Catalysis by electrophilic boronate activation

The ^{11}B NMR spectrum of boronate **1a** gave us the strongest evidence yet that the boron becomes more electrophilic in the presence of an added Lewis acid (Table 4-12). While the spectrum of **1a** displayed a single peak in the absence of scandium, the spectrum of the 1:1 mixture showed two new signals, both upfield of the original signal. The larger of these new signals resonates at 12.8 ppm, and is consistent with the formation of a tetrahedral boronate-acetonitrile complex **23**. This upfield signal does not form in the absence of $Sc(OTf)_3$, nor is it observed if the spectrum is taken in CD_2Cl_2. The third signal, a small, sharp peak at 2.8 ppm, could be due to an activated boronate that has not complexed to acetonitrile. Another ^{11}B NMR spectrum, taken at 128 MHz with 2 equivalents of $Sc(OTf)_3$, is reproduced in Figure 4-13 (page 141).

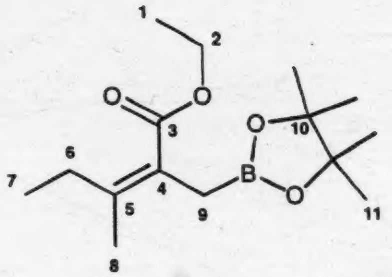


1a **23**

Free Boronate **1a**	Complexed Boronate **23**
33.8	12.8
-	2.8

Table 4-12. ^{11}B NMR shifts for free and complexed boronate **1a** in CD_3CN, 64 MHz.

The ^{1}H and ^{13}C NMR signals for the free and complexed boronate **1a** are shown in Table 4-13. These ^{1}H NMR spectra are reproduced in the experimental section (pages 139-140). The downfield shifts seen in the ^{13}C resonances for the carbons in the unsaturated ester (especially carbons A, B and E) are consistent with the binding of the ester carbonyl to the scandium.[16,17]



^{1}H and ^{13}C NMR Assignments

Signal	^{13}C NMR (100 MHz)		^{1}H NMR (400 MHz)	
	Free **1a**	Complexed **1a**	Free **1a**	Complexed **1a**
1	14.6	14.2	1.23	1.43
2	60.8	70.5	4.09	4.62
3	170.0	181.2		
4	124.7	123.6	-	-
5	147.2	167.8	-	-
6	30.0	29.8	2.33	2.60
7	13.3	13.0	1.00	1.07
8	20.3	23.9	1.74	1.98
9	14.2	19.6	1.76	1.56
10	84.0	84.2	-	-
11	25.0	24.3	1.19	1.36
				6.92[a]
				7.96[a]

Table 4-13. ^{1}H and ^{13}C NMR shifts for boronate **1a** in CD_3CN. Assignments confirmed by 2D NMR techniques. [a] Broad signals due to coordinated water not present in the absence of scandium triflate.

However, the resonances of the carbons and protons around the boron are not as easily interpreted. The chemical shifts for the pinacol carbons (D and G) hardly change at all; the carbon alpha to the boron (carbon J) shifts significantly downfield, and the protons attached to this carbon (protons C) shift upfield. This difference in behavior for the carbon and the protons next to the boron may be explained considering the putative acetonitrile adduct **23**. Binding of the scandium to one or both of the boronate oxygen should make the boron atom more electron deficient, and thus, by induction, the carbon should be shifted downfield. Although it seems counter-intuitive, Denmark and co-workers showed that Lewis acids become more electrophilic after binding to a Lewis base.[18,19] Therefore, the inductive effect of the boron on the α-carbon should become more pronounced after acetonitrile binds to the boron. Meanwhile, the protons might experience a pronounced shielding effect from the p-orbital of the boron, which becomes filled after coordination of the acetonitrile.[20]

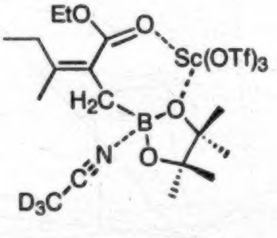


Figure 4-5. Proposed acetonitrile adduct of the complex between scandium – boronate **23**.

Many of the peaks in the NMR spectrum of the complex were significantly broadened, especially the pinacol methyl peaks. If our assumption is correct and the scandium could coordinate to one (or both) of the pinacol oxygens (Figure 4-5), then the four methyl groups on the pinacol ring should become non-equivalent. While we were not able to resolve the peak for the pinacol protons into separate peaks, even at low temperature, the fact that the broadening increases as the temperature decreases is consistent with this theory.

One intriguing result from this NMR study of the 1:1 mixture was that a long-range correlation was observed between the quaternary carbon on the pinacol and one of the coordinated waters. This HMBC correlation suggests that water might be involved in the coordination of scandium to the boronate, and might help to explain why no catalysis is observed with scandium triflate in the presence of molecular sieves. Similarly, Aggarwal and co-workers reported that the rate enhancement in the lanthanum triflate catalysed Baylis-Hillman reaction derives from enhanced hydrogen bonds between the substrate and coordinated hydroxyl groups on the Lewis acid rather than from direct binding of the lanthanide to the substrate (Figure 4-6).[21]

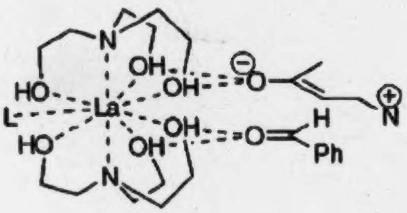
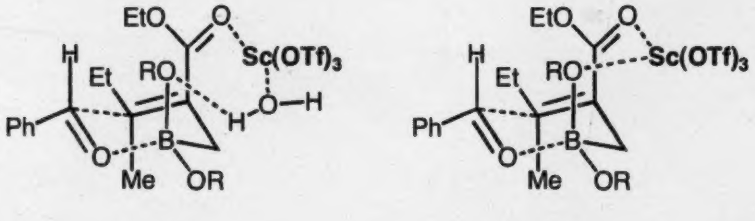


Figure 4-6. Proposed origin of catalytic effect in lanthanum catalysed Baylis-Hillman reaction.[21]

From these NMR studies, we propose that the transition states shown in Figure 4-7 might be responsible for the catalytic effect. These transition states show binding of the scandium to the ester and the boronate oxygen, either directly or via a coordinated water, which is consistent with the observed chemical shift changes described above. This coordination would then increase the Lewis acidity of the boron atom, which then undergoes enhanced allylboration with an aldehyde via the usual Zimmerman-Traxler transition state.

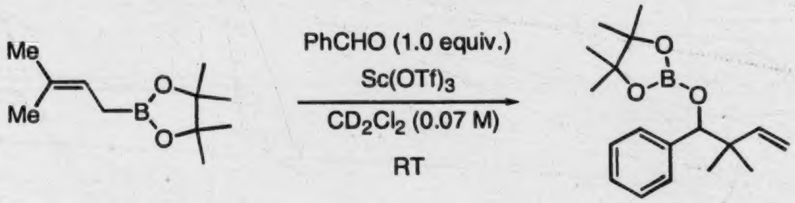


A **B**

Figure 4-7. Proposed transition states for the scandium catalysed allylboration with boronate **1a** and benzaldehyde.

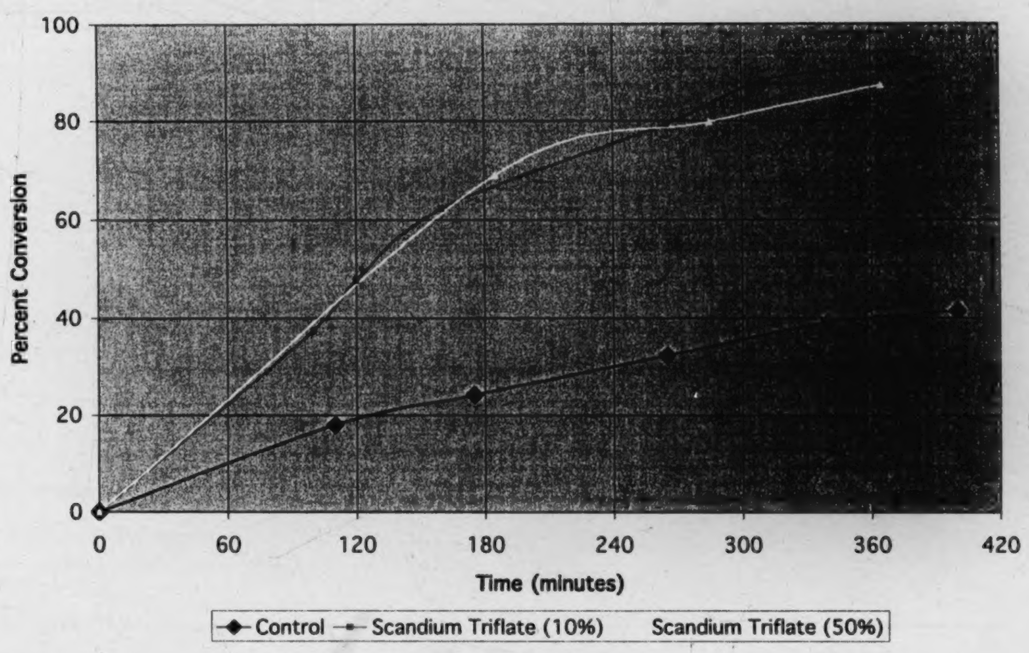
As usual, this mechanistic hypothesis must be taken with a grain of salt, since the complex observed between scandium and the boronate **1a** in the absence of aldehyde does not necessarily reflect what occurs between these three species in the transition state. Also, the role of the carboxylic ester in the catalysis is not clear. Studies both in our lab and in others[4] have shown that boronates which lack this ester (*e.g.*, **6d**) also undergo a metal-catalysed allylboration reaction (Graph 4-6). However, the magnitude of the catalysis observed at room temperature is much smaller with these boronates (approximately a 3 fold rate increase) than with boronate **1a** (35 fold increase). This result might simply reflect the large difference in reactivity between boronates **1a** and **6d** (compare the time scale on Graph 4-6 to those on the graphs in Section 4.4.1). Alternatively, it might suggest that the ester in

1a acts as a second coordination site for the catalyst, thereby increasing the binding of the boronate to the catalyst and allowing for greater activation to occur.



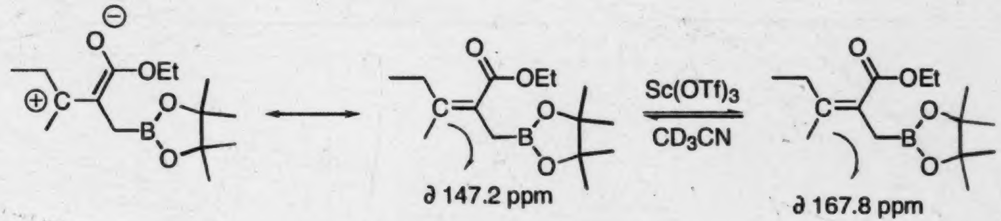
6d **24**

Graph 4-6. Catalysed reactions with a boronate that lacks the α-carboxyester group. Reaction monitored by ^{1}H NMR (400 MHz).



4.4.4.3.2 *Catalysis by ester deconjugation*

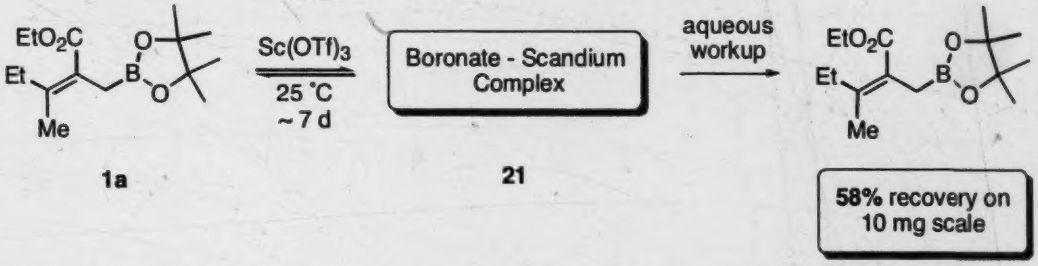
Another possible mode of catalysis is that coordination of the scandium to the boronate might cause the ester to twist out of conjugation with the olefin, thus rendering the γ-carbon more nucleophilic in the complex than in the free boronate (Scheme 4-18). However, the ^{13}C NMR spectrum of the 1:1 mixture of **1a** and scandium triflate showed that the signal for the γ-carbon shifts downfield by 20 ppm in the complex (Table 4-13, page 132), suggesting that it is significantly more electron deficient in the complex than in the free boronate. This result is not consistent with a Lewis acid induced increase in nucleophilicity of this carbon, and consequently it is unlikely that this proposal is the root of the observed catalytic effect. Furthermore, the presence of a carboxylic ester is not required for catalysis to occur (see Section 4.4.4.3.1)



Scheme 4-18

4.4.4.3.3 Catalysis by transmetalation

While some catalysed allylstannation reactions are reported to proceed via transmetalation of the initial allylmetal to a more reactive allylmetal species,[22] there are no known examples of an allylboration that proceeds via a similar mechanism. Boron to palladium transmetalation is well known,[23] but there are no know reports of a boron to scandium, copper or ytterbium transmetalation. In this current study, we were able to treat a solution of boronate **1a** with excess scandium triflate, find evidence for the formation of a complex between the metal and the boronate by ^{1}H NMR, and then afterwards recover the boronate unchanged and in good yield (Scheme 4-19). This recovery shows that no transmetalation of the boronate had occurred during the experiment.



Scheme 4-19

4.4.4.3.4 Catalysis via aldehyde double coordination

A final mechanism of catalysis that we considered is the double activation of the aldehyde by coordination to both the boronate and the scandium in the transition state (Figure 4-8). We believe that this possibility is unlikely because the simultaneous coordination of both lone pairs on an aldehyde to two Lewis acids is a very rare event. Although there have been several reports of aldehyde double coordination, these examples all featured specialized, bidentate Lewis acids.[7] Also, aldehyde double coordination can not explain the downfield shifts observed in the resonances of the ester and olefin carbons. However, the transition state structure of the catalysed allylboration reaction may not necessarily resemble the complex formed between the boronate and scandium in the absence of aldehyde. So, as unlikely as aldehyde double coordination may appear, it would be premature to eliminate this possibility at this stage of the project.

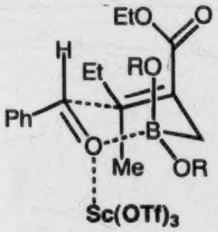


Figure 4-8. Possible Transition State of an allyboration featuring a doubly coordinated aldehyde.

4.5 Experimental

4.5.1 General

The methods described in Section 2.3.1 (page 34) also apply here, with the following additions. Boronates **1**, **14** and **15** were prepared according to the procedures outlined in Chapters 2 and 3. Boronate **6d** was prepared according to the procedure of Hoffmann and Schlapbach.[24] All aldehydes were purified by Kugelrohr distillation prior to use. All other chemicals were purchased from commercial sources and used as received. Chiral HPLC analysis was performed using a CHIRALPAK AD-RH column (0.46 cm x 15 cm) with UV detection at 210 nm.

4.5.2 General procedure for NMR catalyst search

The reaction with scandium triflate is representative. An NMR tube was charged with $Sc(OTf)_3$ (9 mg, 0.02 mmol) and dried overnight under vacuum at 130 °C. Benzaldehyde (5 μL, 0.05 mmol) was then added, followed by a 0.07 M solution of boronate **1a** in CD_2Cl_2 (0.75 mL, 0.053 mmol). ^1H and ^{11}B NMR spectra were recorded daily for 7 days. The quartet at 4.14 ppm (O-CH_2-Me for boronate **1a**) and the singlet at

6.32 ppm (olefin proton for lactone **2a**) were used as reference peaks in the proton spectra. Some ^{1}H spectra were complicated by the paramagnetic nature of some of the catalysts. To remove any adventitious triflic acid, one NMR reaction was run using Sc(OTf)$_3$, boronate **1a** (12.8 mg in 0.75 mL of CD_2Cl_2), benzaldehyde (4.5 μL, 0.044 mmol), and diisopropylamine (4.2 μL, 0.024 mmol).

Studies with boronate **6d** were performed in an analogous manner, except that the spectra were recorded every hour for 7 hours, reflecting the increased reactivity of these boronates.

The half-life reaction time between Sc(OTf)$_3$-catalyzed and uncatalysed runs in the case of control allylboronate **6d** was taken directly from the graph found in Section 4.4.4.3.1. In the case of allylboronate **1a**, the data for the background uncatalysed run were extrapolated from an expanded version of Graph 4-1, page 110, and assumed plot linearity. This analysis constitutes an underestimation given the expected exponential shape of the plot. These data were collected under the NMR screening conditions described previously of 50 mol% Sc(OTf)$_3$.

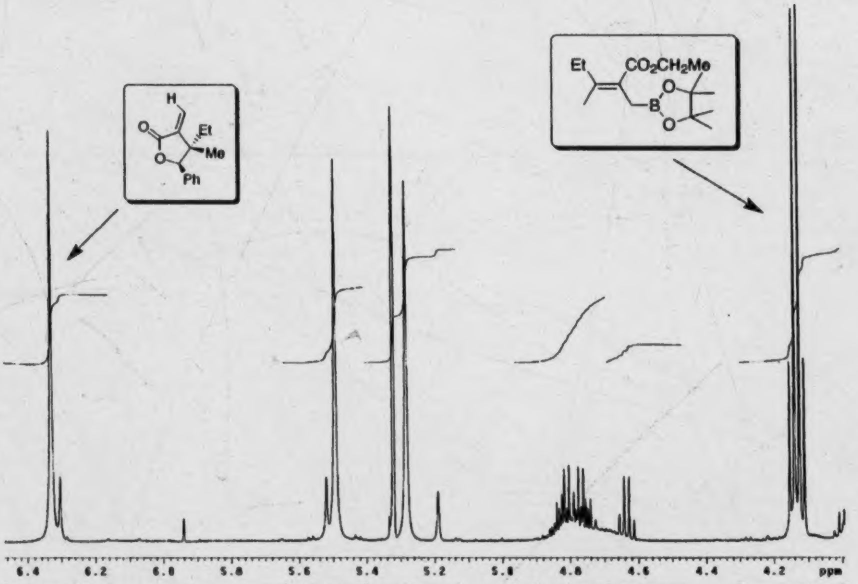


Figure 4-9. Representative ^{1}H NMR Spectrum for **1a/2a** (CD_2Cl_2, 500 MHz).

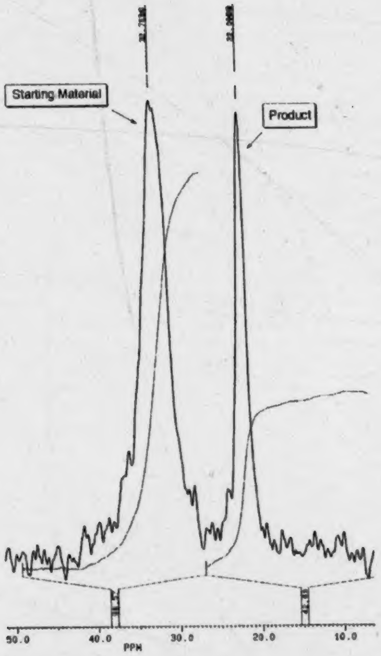


Figure 4-10. Representative ^{11}B NMR Spectrum for **1a/8** (CD_2Cl_2, 64 MHz).

4.5.3 ^{1}H NMR spectra of a 1:1 mixture of 1a and $Sc(OTf)_3$

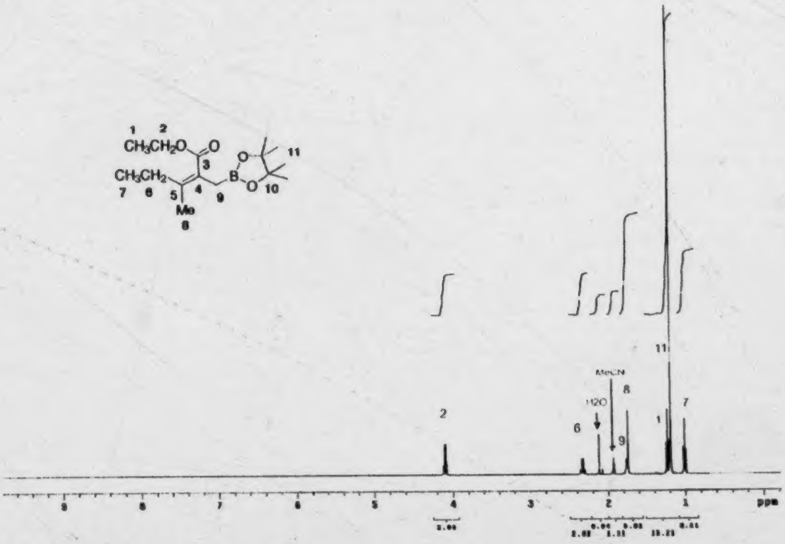


Figure 4-11. ^{1}H NMR of Boronate **1a** in CD_3CN (400 MHz).

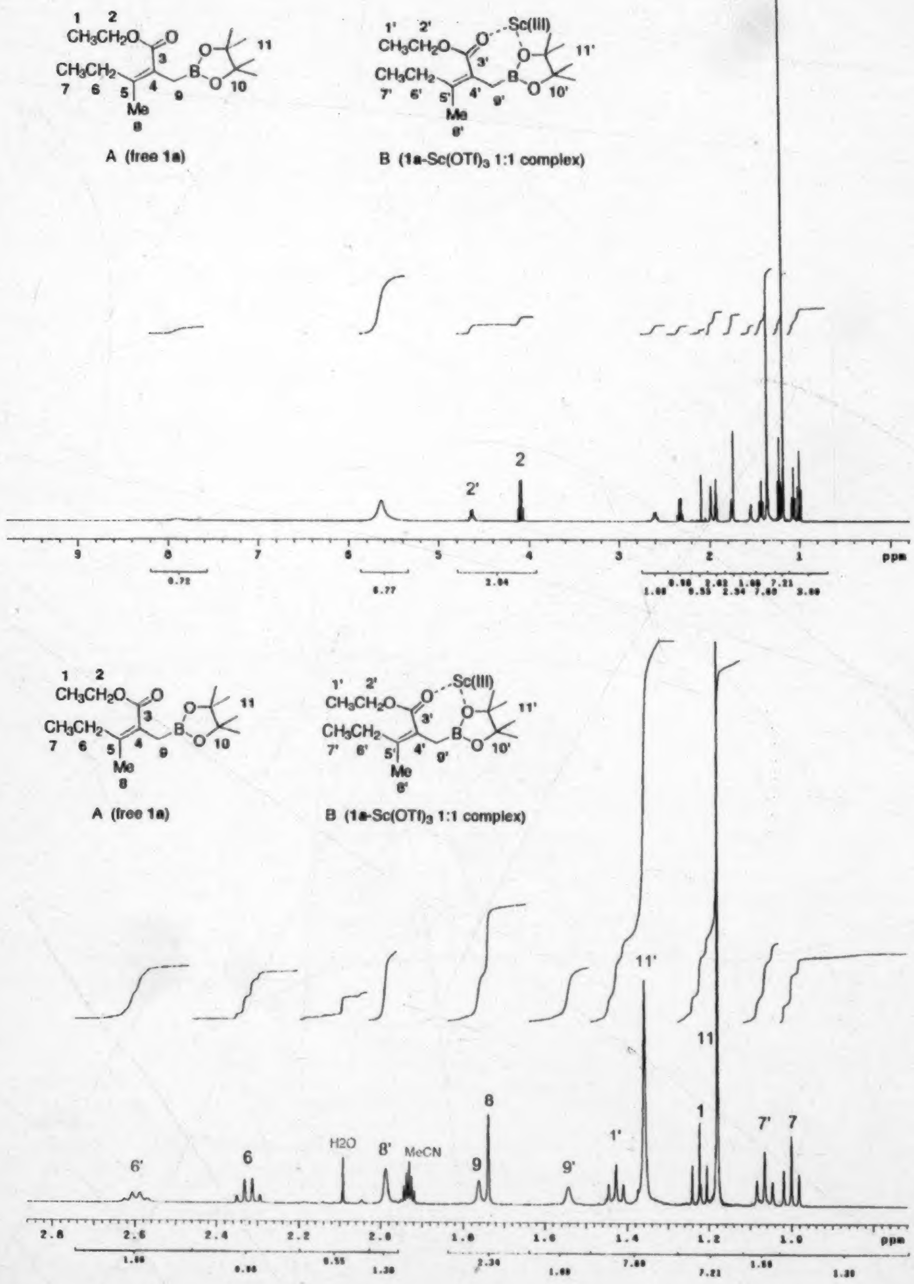


Figure 4-12. ^{1}H NMR of Boronate **1a** with 1 equiv. Sc(OTf)$_3$ in CD$_3$CN (400 MHz) with expansion. The structure of the boronate:scandium complex shown is hypothetical.

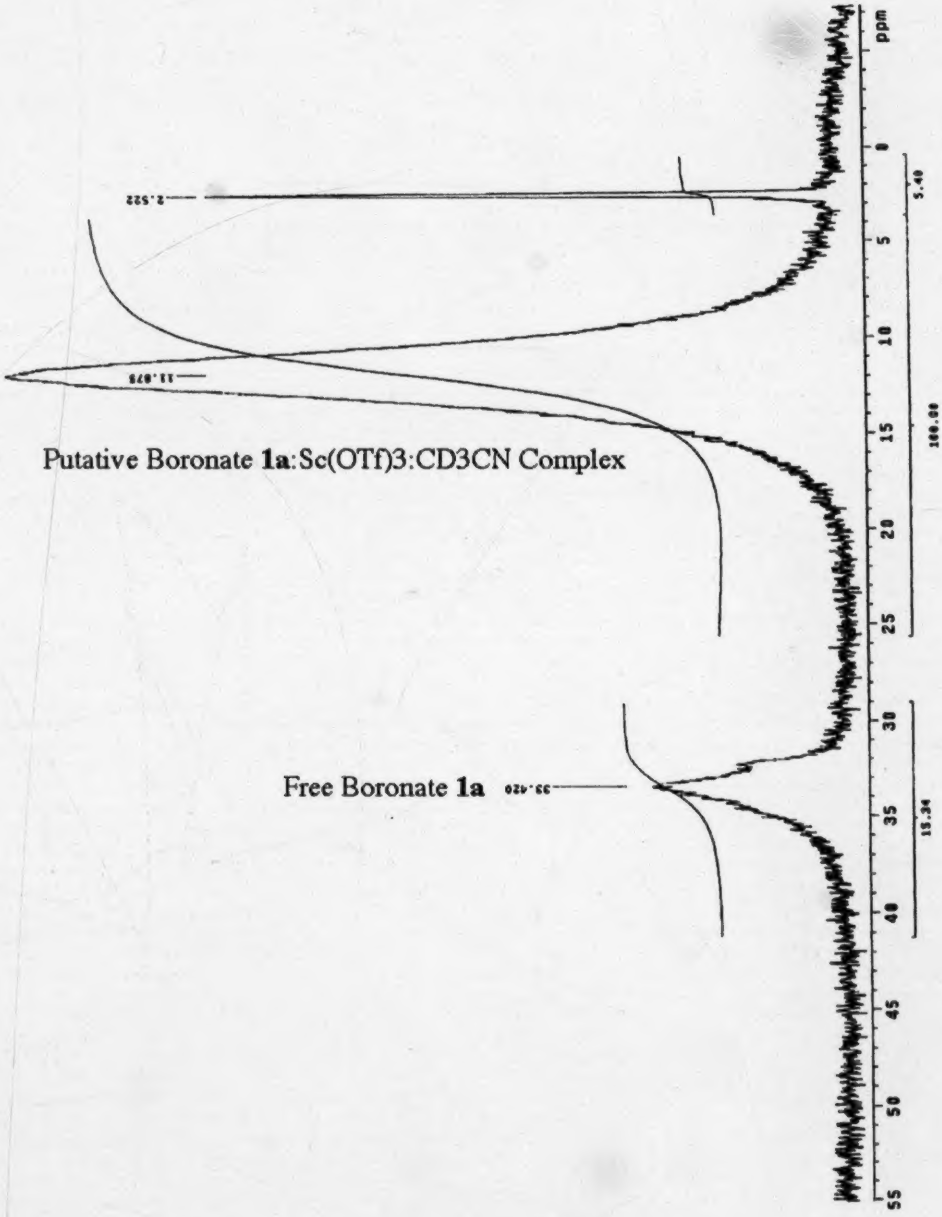


Figure 4-13. ^{11}B NMR of Boronate **1a** with 2 equiv. Sc(OTf)$_3$ in CD$_3$CN (128 MHz).

4.5.4 Preparation of aromatic lactones 2

4.5.4.1 *(4R*, 5S*)-4-Ethyl –4-methyl-3-methylene-5-phenyl-dihydro-furan-2-one 2a*

A slurry of boronate **1a** (140 mg, 0.495 mmol), benzaldehyde (55 mg, 0.52 mmol) and $Sc(OTf)_3$ (25 mg, 0.052 mmol) were stirred in toluene (0.5 mL) at RT under Argon for 24 h. The mixture was then diluted with NH_4Cl/NH_4OH (9:1, v/v, 5 mL) and extracted with Et_2O (3 x 5 mL). The combined extractions were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the product (99 mg, 0.46 mmol, 93%). Similarly, reactions using $Cu(OTf)_2$ and $Yb(OTf)_3$ gave the product in yields of 67% and 91% respectively after flash chromatography. The spectroscopic data for this compound were identical to that described in Section 3.3.1.7 (page 73).

4.5.4.2 *(4R*, 5S*)-5-(4-Acetoxyphenyl)-4-ethyl-4-methyl-3-methylene-dihydro-furan-2-one 2b*

A solution of boronate **1a** (62 mg, 0.22 mmol) and *p*-acetoxybenzaldehyde (33 mg, 0.20 mmol) in toluene (0.2 mL) was treated with $Sc(OTf)_3$ (12 mg, 0.024 mmol) and stirred at RT under Ar for 18 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (71 mg). Flash chromatography (2.5% Acetone/Toluene, 4 g SiO_2) gave the product (35 mg, 0.13 mmol, 64%), which was further purified by Kugelrohr distillation (250 °C, 0.1 torr) to give the pure lactone (32 mg, 0.12 mmol, 57%).

TLC (2.5% Acetone/Toluene, UV/$KMnO_4$): 0.21; ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (AB, $J = 8.3$ Hz, 2H), 7.07 (AB, $J = 8.3$ Hz, 2H), 6.34 (s, 1H), 5.45 (s, 1H), 5.25 (s, 1H), 2.27 (s, 3H), 1.68 (m, 2H), 0.96 (t, $J = 7.5$ Hz, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.0, 150.5, 142.6, 134.4, 127.0, 121.7, 121.5, 85.7, 47.0, 33.4, 22.6, 21.2, 8.6; Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.04; H, 6.63. Found: C, 69.62; H, 6.40.

4.5.4.3 *(4R*, 5R*)-4-Butyl-5-(3-iodophenyl)-4-methyl-3-methylene-dihydro-furan-2-one 2c*

A solution of boronate **1b** (124 mg, 0.401 mmol) and *m*-iodobenzaldehyde (142 mg, 0.614 mmol) in toluene (0.4 mL) was treated with $Sc(OTf)_3$ (20 mg, 0.041 mmol). The resulting slurry was stirred at RT under Ar for 24 h. Reaction was then diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (280 mg). Flash chromatography (1% EtOAc/Toluene, 30 g SiO_2) gave the product (82 mg, 0.22 mmol, 55%), which was further purified by Kugelrohr distillation (250 °C, 0.1 torr) to give the pure lactone (72 mg, 0.194 mmol, 48%).

TLC (1% EtOAc/Toluene, $KMnO_4$): 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (m, 2H), 7.27 (m, 1H), 7.11 (apparent t, J = 7.8 Hz, 1H) 6.32 (s, 1H), 5.50 (s, 1H), 5.06 (s, 1H), 1.32 (s, 3H), 1.15-0.90 (m, 5H), 0.78 (m, 1H), 0.73 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 143.3, 137.4, 137.2. 134.9, 130.0, 125.3, 121.4, 94.1, 87.3, 46.9, 34.3, 25.0, 22.8, 21.6, 13.8; IR (CH_2Cl_2 cast, cm^{-1}): 2957, 1770, 1660, 1592, 1119; HRMS (EI, *m/z*) Calcd for $C_{16}H_{19}O_2I$: 370.04297. Found: 370.04344.

4.5.4.4 (4R*, 5S*)-4-Butyl-4-methyl-3-methylene-5-pentafluorophenyl-dihydro-furan-2-one 2d

A solution of boronate **1b** (132 mg, 0.424 mmol) and pentafluorobenzaldehyde (132 mg, 0.674 mmol) in toluene (0.4 mL) was treated with $Sc(OTf)_3$ (21 mg, 0.043 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (212 mg). Flash chromatography (1% EtOAc/Toluene, 22 g SiO_2) gave the product (75 mg, 0.22 mmol, 53%), which was further purified by Kugelrohr distillation (250 °C, 0.1 torr) to give the pure lactone (66 mg, 0.198 mmol, 47%).

TLC (1% EtOAc/Toluene, $KMnO_4$): 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 1H), 5.57 (s, 1H), 5.48 (s, 1H), 1.55 (dt, J = 13.3 Hz, 4.2 Hz, 1H), 1.35 (s, 3H), 1.35-0.90 (m, 5H), 0.75 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 146.3 and 143.8,[a] 142.7, 142.6 and 140.1,[a] 139.0 and 136.5,[a] 121.6, 110.3,[a] 80.6, 46.2, 34.5, 25.5, 24.6, 22.9, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -139.6 (br s, 2F), -152.3 (tt, J = 20.9 Hz, 2.6 Hz, 1F), -161.1 (dt, J = 22.1 Hz, 8.0 Hz, 2F); IR (CH_2Cl_2 cast, cm^{-1}): 2960, 1781, 1655, 1130; HRMS (ES, *m/z*) Calcd for $C_{16}H_{15}F_5O_2Na$: 357.088991. Found: 357.088836; Anal. Calcd for $C_{16}H_{15}F_5O_2$: C, 57.48; H, 4.53. Found: C, 57.40; H, 4.42.

4.5.4.5 (4R*, 5R*)-4-Butyl-4-methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one 2e

A solution of boronate **1b** (132 mg, 0.424 mmol) and *p*-nitrobenzaldehyde (72 mg, 0.47 mmol) in toluene (0.5 mL) was treated with $Sc(OTf)_3$ (22 mg, 0.046 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (154 mg). Flash chromatography (1% EtOAc/Toluene, 16 g SiO_2) gave the pure product (71 mg, 0.25 mmol, 58%). The spectroscopic data for this compound were identical to that described in Section 3.3.1.4 (page 71).

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[a] These signals are complex, broad patterns due to ^{13}C-^{19}F splitting. They are well resolved singlets at 145.1, 141.4, 137.7 and 110.2 ppm respectively in ^{19}F decoupled spectra.

4.5.4.6 (4R*, 5S*)-4-Butyl-4-methyl-3-methylene-5-(1-naphthyl)-dihydro-furan-2-one 2f

A solution of boronate **1b** (124 mg, 0.399 mmol) and 1-naphthaldehyde (56 mg, 0.36 mmol) in toluene (0.4 mL) was treated with Sc(OTf)$_3$ (14 mg, 0.28 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (105 mg). Flash chromatography (25% Et$_2$O/Hexanes, 9 g SiO$_2$) gave the pure product (46 mg, 0.16 mmol, 44%).

TLC (25% Et$_2$O/Hexanes, UV/KMnO$_4$): 0.24; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.88 (m, 1H), 7.85 (m, 1H), 7.83 (m, 1H), 7.61 (m, 1H), 7.45 (m, 3H), 6.37 (s, 1H), 6.08 (s, 1H), 5.53 (s, 1H), 1.43 (s, 3H), 1.22 (m, 1H), 0.94 (m, 3H), 0.76 (m, 2H), 0.61 (t, J = 7.2 Hz, 3H);^{13}C NMR (125 MHz, CDCl$_3$): δ 170.6, 144.2, 133.7, 130.9, 130.7, 129.1, 128.9, 126.2, 125.6, 125.3, 125.1, 123.0, 121.2, 84.9, 47.6, 34.8, 25.1, 22.8, 22.7, 13.7; Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.58; H, 7.55. Found: C, 81.23; H, 7.57.

4.5.4.7 (4R*, 5R*)-4-Butyl-4-methyl-3-methylene-5-(4-tolyl)-dihydro-furan-2-one 2g

A solution of boronate **1b** (118 mg, 0.424 mmol) and *p*-tolualdehyde (66 mg, 0.55 mmol) in toluene (0.4 mL) was treated with Sc(OTf)$_3$ (18 mg, 0.037 mmol) and stirred at RT under Ar for 19 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (130 mg). Flash chromatography (1% EtOAc/Toluene, 15 g SiO$_2$) yielded the pure product (73 mg, 0.28 mmol, 75%).

TLC (1% EtOAc/Toluene, UV/KMnO$_4$): 0.41; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.17 (s, 5H), 6.30 (s, 1H), 5.47 (s, 1H), 5.10 (s, 1H), 2.35 (s, 3H), 1.30 (s, 3H), 1.02 (m, 5H), 0.80 (m, 1H), 0.71 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.5, 144.0, 138.0, 131.8, 128.9, 126.0, 120.8, 88.6, 46.9, 34.1, 25.1, 22.8, 21.4, 21.1, 13.8; HRMS (EI, *m/z*) Calcd for $C_{17}H_{22}O_2$: 258.16199. Found: 258.16159; Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.02; H, 8.60. Found: C, 78.18; H, 8.74.

4.5.4.8 (4R*, 5S*)-5-(4-Bromophenyl)-4,4-dimethyl-3-methylene-dihydro-furan-2-one 2h

A solution of boronate **1c** (105 mg, 0.39 mmol) and *p*-bromobenzaldehyde (63 mg, 0.34mmol) in toluene (0.4 mL) was treated with Sc(OTf)$_3$ (18 mg, 0.037 mmol) and stirred at RT under Ar for 19 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (115 mg). Flash chromatography (5% EtOAc/Toluene, 9 g SiO_2) yielded the pure product (60 mg, 0.22 mmol, 62%).

TLC (5% EtOAc/Toluene, UV/$KMnO_4$): 0.40; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (AB, *J* = 8.5 Hz, 2H), 7.14 (AB, *J* = 8.7 Hz, 2H), 6.28 (s, 1H), 5.56 (s, 1H), 5.10 (s, 1H), 1.38 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 145.1, 134.8, 131.6, 127.5, 122.4, 120.5, 87.3, 43.5, 25.7, 24.3; IR (CH_2Cl_2 cast, cm^{-1}): 2966, 1770, 1660, 1594, 1118, 814; HRMS (EI, *m/z*) Calcd for $C_{13}H_{13}O_2{}^{81}Br$: 282.00784. Found: 282.00818; Calcd for $C_{13}H_{13}O_2{}^{79}Br$: 280.00989. Found: 280.00991.

4.5.4.9 (4R*, 5S*)-4-Butyl-5-(2-methoxyphenyl)-4-methyl-3-methylene-dihydro-furan-2-one 2i

A solution of boronate **1a** (97 mg, 0.34 mmol) and *o*-anisaldehyde (44 mg, 0.32 mmol) in toluene (0.4 mL) was treated with $Sc(OTf)_3$ (14 mg, 0.030 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (66 mg). ^{1}H NMR (500 MHz, $CDCl_3$) showed that the product was a 2:1 mixture of diastereomers.

4.5.4.10 (4R*, 5S*)-4-Ethyl-4-methyl-3-methylene-5-(Z-2-phenylethenyl)-dihydro-furan-2-one 2j

A solution of boronate **1a** (123 mg, 0.434 mmol) and cinnamaldehyde (60 mg, 0.46 mmol) in toluene (0.4 mL) was treated with $Sc(OTf)_3$ (21 mg, 0.043 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (144 mg). ^{1}H NMR (500 MHz, $CDCl_3$) showed that the product was a 1.5:1 mixture of diastereomers .

4.5.4.11 (4R*, 5S*)-4-Ethyl-4-methyl-3-methylene-5-[Z-2-(4-nitrophenyl)-ethenyl]-dihydro-furan-2-one 2k

A solution of boronate **1a** (82 mg, 0.29 mmol) and 4-nitrocinnamaldehyde (52 mg, 0.30 mmol) in toluene (0.3 mL) was treated with $Sc(OTf)_3$ (15 mg, 0.030 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (103 mg). ^{1}H NMR (500 MHz, $CDCl_3$) showed that the product was a 2.8:1 mixture of diastereomers favouring the expected isomer.

A diastereomerically pure sample was prepared by refluxing a solution of boronate **1a** (103 mg, 0.364 mmol) and 4-nitrocinnamaldehyde (51 mg, 0.29 mmol) in toluene (0.7 mL) under Ar for 18 h. Concentration of the mixture (125 mg crude) followed by flash chromatography (25% EtOAc/Hexanes, 7 g silica) yielded the pure lactone (68 mg, 0.23 mmol, 82%).

TLC (25% EtOAc/Hexanes, UV/$KMnO_4$): 0.32; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (AB, *J* = 8.8 Hz, 2H), 7.50 (AB, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 15.8 Hz, 1H), 6.32 (s, 1H), 6.25 (dd, *J* = 16.0 Hz, 6.7 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 1H), 4.84 (dd, *J* = 6.7 Hz, 1.2 Hz, 1H), 1.67 (m, 2H), 1.12 (s, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 147.4, 142.8, 142.1, 131.0, 129.1, 127.3, 124.0, 121.7, 84.7, 46.5, 32.8, 21.4, 8.4; IR (CH_2Cl_2 cast, cm^{-1}): 2969, 1764, 1655, 1596, 1517, 1343, 1108, 971, 815; HRMS (EI, *m/z*) Calcd for $C_{16}H_{19}NO_4$: 289.13141. Found: 289.13096; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.88; H, 5.98; N, 4.88. Found: C, 66.82; H, 5.92; N, 4.74.

4.5.4.12 (4R, 5R*)-4-Butyl-5-(4-methoxyphenyl)-4-methyl-3-methylene-dihydro-furan-2-one 2l*

A solution of boronate **1b** (135 mg, 0.434 mmol) and *p*-anisaldehyde (90 mg, 0.66 mmol) in toluene (0.9 mL) was treated with $Sc(OTf)_3$ (22 mg, 0.044 mmol) and stirred at RT under Ar for 16 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (190 mg). ^{1}H NMR (500 MHz, $CDCl_3$) showed that the product was a 1.8:1 mixture of diastereomers favouring the expected isomer.

A diastereomerically pure sample of **2l** was prepared by refluxing a solution of boronate **1b** (112 mg, 0.360 mmol) and *p*-anisaldehyde (45 mg, 0.33 mmol) in toluene (1 mL) under Ar for 24 h. Concentration of the mixture followed by flash chromatography (25% Et_2O/Hexanes, 11 g silica) yielded the pure lactone (56 mg, 0.20 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (AB, *J* = 8.9 Hz, 2H), 6.89 (AB, *J* = 8.7 Hz, 2H), 6.29 (s, 1H), 5.44 (s, 1H), 5.08 (s, 1H), 3.81 (s, 3H), 1.28 (s, 3H), 1.15-0.90 (m, 5H), 0.79 (m, 1H), 0.71 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 159.5, 144.0, 127.4, 126.8, 120.8, 113.6, 88.5, 55.3, 47.0, 34.2, 25.2, 23.0, 21.6, 13.9; IR (CH_2Cl_2 cast, cm^{-1}): 2958, 1769, 1659, 1613, 1251, 817; HRMS (EI, *m/z*) Calcd for $C_{17}H_{22}O_3$: 274.15689. Found: 274.15514.

4.5.4.13 (4R, 5R*)-4-Butyl-4-methyl-3-methylene-5-(E-1-propenyl)-dihydro-furan-2-one 2m*

A solution of boronate **1b** (129 mg, 0.416 mmol) and crotonaldehyde (43 mg, 0.61 mmol) in toluene (0.8 mL) was treated with $Sc(OTf)_3$ (21 mg, 0.044 mmol) and stirred at RT under Ar for 20 h. Work up as described in Section 4.5.4.2 gave the crude product as a 1.6:1 mixture of diastereomers (137 mg), which could be separated by flash chromatography (5% Et_2O/Hexanes, 10 g silica).

Major Isomer: (4*R**, 5*R**)-**2m**, 32 mg, 0.15 mmol, 36%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 (s, 1H), 5.82 (m, 1H), 5.49 (m, 1H), 5.39 (s, 1H), 4.38 (d, *J* = 8.1 Hz, 1H), 1.76 (m, 3H), 1.4-1.1 (m, 6H), 1.13 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 144.0, 132.5, 124.0, 120.2, 88.5, 46.1, 34.7, 25.6, 23.1, 21.7, 18.0, 14.0; IR (CH_2Cl_2 cast, cm^{-1}): 2959, 1766, 1661, 1106, 968; HRMS (EI, *m/z*) Calcd for $C_{13}H_{20}O_2$: 208.14633. Found: 208.14593; Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.94; H, 9.70. Found: C, 74.85; H, 9.57.

Minor Isomer: (4*R**, 5*S**)-**2m**, 27 mg, 0.099 mmol, 23%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (s, 1H), 5.77 (m, 1H), 5.40 (s, 1H), 5.36 (m, 1H), 4.56 (d, *J* = 8.2 Hz, 1H), 1.72 (m, 3H), 1.48 (m, 2H), 1.30-1.15 (m, 4H), 1.04 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 144.0, 131.4, 126.0, 120.4, 86.5, 45.5, 40.0, 26.1, 23.2, 21.8, 17.9, 14.0; IR (CH_2Cl_2 cast, cm^{-1}): 2960, 1766, 1661, 1105, 966; HRMS (EI, *m/z*) Calcd for $C_{13}H_{20}O_2$: 208.14633. Found: 208.14616; Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.94; H, 9.70. Found: C, 74.97; H, 9.89.

4.5.4.14 (4R, 5S*)-3-Butyl-3-ethyl-4-methylene-3,4-dihydro-2H-[2,2']bifuranyl-5-one 2n*

A solution of boronate **1c** (130 mg, 0.402 mmol) and furfural (38 mg, 0.40 mmol) in toluene (0.4 mL) was treated with $Sc(OTf)_3$ (20 mg, 0.04 mmol) and stirred at RT under Ar for 24 h. Work up as described in Section 4.5.4.2 gave the product as a crude oil (116 mg). ^{1}H NMR (500 MHz, $CDCl_3$) showed that the product was a 2.5:1 mixture of diastereomers favouring the expected isomer.

A diastereomerically pure sample of **2n** was prepared by refluxing a solution of boronate **1c** (136 mg, 0.419 mmol) and furfural (40 mg, 0.42 mmol) in toluene (0.8 mL) under Ar for 24 h. Concentration of the mixture followed by flash chromatography (2.5% EtOAc/Toluene, 26 g silica) yielded the pure lactone (78 mg, 0.31 mmol, 74%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 1H), 6.35 (s, 1H), 6.33 (m, 1H), 6.31 (m, 1H), 5.42 (s, 1H), 5.18 (s, 1H), 1.71 (m, 2H), 1.48 (m, 1H), 1.24-0.96 (m, 5H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.74 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 149.9, 142.8, 141.5, 121.5, 110.3, 109.4, 81.3, 50.0, 31.6, 28.8, 25.3, 23.0, 13.7, 7.6; Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.54; H, 8.13. Found: C, 72.45; H, 8.41.

4.5.4.15 (4R, 5R*)-4-Butyl-4-ethyl-3-methylene-5-(4-methylthiophenyl)-dihydro-furan-2-one 2o*

A solution of boronate **1c** (137 mg, 0.421 mmol) and 4-methylthiobenzaldehyde (65 mg, 0.43 mmol) in toluene (0.4 mL) was treated with $Sc(OTf)_3$ (21 mg, 0.043 mmol) and stirred at RT under Ar for 7 d. Work up as described in Section 4.5.4.2 gave the product as a crude oil (135 mg). ^{1}H NMR (500 MHz, $CDCl_3$) showed that the product was a 2.5:1 mixture of diastereomers.

4.5.5 Catalysed allylborations with aliphatic aldehydes – First Generation method

4.5.5.1 (4R, 5S*)-4-Ethyl-4-methyl-3-methylene-5-phenethyl-dihydro-furan-2-one 9a*

A solution of boronate **1a** (103 mg, 0.365 mmol) and hydrocinnamaldehyde (74 mg, 0.55 mmol) in toluene (0.6 mL) was treated with $Sc(OTf)_3$ (20 mg, 0.041 mmol) and stirred at RT under Ar for 24 h. Reaction was then diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (145 mg). Flash chromatography (10% Et_2O/Hexanes, 7 g SiO_2) gave the pure product (57 mg, 0.23 mmol, 64%). Similarly, use of $Yb(OTf)_3$ instead of scandium triflate afforded the product in 66% yield.

TLC (1% EtOAc/Toluene, $KMnO_4$): 0.26; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.18 (m, 3H), 6.23 (s, 1H), 5.41 (s, 1H), 4.17 (dd, *J* = 10.8 Hz, 2.9 Hz), 2.94 (m, 1H), 2.68 (m, 1H), 1.78 (m, 2H), 1.52 (m, 2H), 1.08 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 144.0, 141.0, 128.5, 126.1, 120.6, 84.4, 45.0, 33.6, 32.8, 32.3, 20.2, 8.3; IR (CH_2Cl_2 cast, cm^{-1}): 3061, 2967, 1762, 1659, 1602, 1113, 751, 700; HRMS (EI, *m/z*) Calcd for $C_{16}H_{22}O_2$: 244.14633. Found: 244.14648; Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.64; H, 8.27. Found: C, 78.28; H, 8.38.

4.5.5.2 (4R, 5R*)-5-Benzyloxymethyl-4-ethyl-4-methyl-3-methylene-dihydro-furan-2-one 9b*

A solution of boronate **1a** (93 mg, 0.33 mmol) and benzyloxyacetaldehyde (74 mg, 0.49 mmol) in toluene (0.7 mL) was treated with $Sc(OTf)_3$ (19 mg, 0.031 mmol) and stirred at RT under Ar for 24 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (98 mg). Flash chromatography (25% Et_2O/Hexanes, 10 g SiO_2) followed by Kugelrohr distillation (250 °C, 0.1 torr) gave the pure product (44 mg, 0.17 mmol, 52%).

TLC (25% Et_2O/Hexanes, $KMnO_4$): 0.19; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.26 (m, 3H), 6.19 (s, 1H), 5.37 (s, 1H), 4.52 (s, 2H), 4.32 (t, *J* = 4.5 Hz, 1H), 3.60 (dq, *J* = 10.8 Hz, 4.3 Hz, 2H), 1.55 (m, 2H), 1.18 (s, 3H), 0.85 (t, *J* = 7.5 Hz, 3H); IR (CH_2Cl_2 cast, cm^{-1}): 3030, 2968, 1764, 1657, 1105, 737, 697; HRMS (EI, *m/z*) Calcd for $C_{16}H_{20}O_3$: 260.14124. Found: 260.14190; Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.80; H, 7.76. Found: C, 73.46; H, 7.96.

4.5.5.3 (4R*, 5S*)-4-Ethyl-5 -4-methyl-3-methylene-5-(2-methylpropyl) -dihydro-furan-2-one 9c

A solution of boronate **1a** (84 mg, 0.30 mmol) and isovaleraldehyde (24 mg, 0.28 mmol) in toluene (0.6 mL) was treated with $Sc(OTf)_3$ (15 mg, 0.030 mmol) and stirred at RT under Ar for 12 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (79 mg). Flash chromatography (50% CH_2Cl_2/Hexanes, 4 g SiO_2) gave the pure product (25 mg, 0.13 mmol, 46%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (s, 1H), 5.40 (s, 1H), 4.26 (dd, *J* = 11.4 Hz, 2.4 Hz, 1H), 1.88 (m, 1H), 1.55 (m, 2H), 1.44 (ddd, *J* = 14.2 Hz, 11.4 Hz, 4.1 Hz, 1H), 1.21 (ddd, *J* = 14.2 Hz, 9.7 Hz, 2.4 Hz, 1H), 1.06 (s, 3H), 0.94 (dd, *J* = 6.7 Hz, 1.4 Hz, 6H), 0.86 (t, *J* = 7.5 Hz, 3H);

4.5.5.4 (4R*, 5S*)-5-Cyclohexyl-4-ethyl-4-methyl-3-methylene-dihydro-furan-2-one 9d

A solution of boronate **1a** (126 mg, 0.405 mmol, 10:1 *Z*:*E* mixture) and cyclohexanecarboxaldehyde (111 mg, 0.394 mmol) in toluene (0.75 mL) was treated with $Cu(OTf)_2$ (15 mg, 0.043 mmol) and stirred at 60 °C under Ar for 16 h. Reaction was then brought to RT, diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (164 mg). Flash chromatography (1% EtOAc/Toluene, 10 g SiO_2) gave the pure product (47 mg, 0.21 mmol, 54%) as an inseparable 10:1 mixture of diastereomers. TLC (1% EtOAc/Toluene, $KMnO_4$): 0.20; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.33 (s, 1H), 3.97 (d, *J* = 4.2 Hz, 1H), 1.80-1.45 (m, 8H), 1.4-1.0 (m, 5H), 1.17 (s, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 144.1, 118.9, 89.1, 45.2, 40.0, 34.4, 30.9, 27.4, 26.4, 26.1, 25.7, 19.9, 8.2; IR (CH_2Cl_2 cast, cm^{-1}): 3093, 2928, 1765, 1655, 1111; HRMS (EI, *m/z*) Calcd for $C_{14}H_{22}O_2$: 222.16199. Found: 222.16219.

4.5.5.5 (4R*, 5R*)-4-Butyl-5-cyclohexyl-4-methyl-3-methylene-dihydro-furan-2-one 9e

A solution of boronate **1b** (109 mg, 0.382 mmol) and cyclohexanecarboxaldehyde (62 mg, 0.55 mmol) in toluene (0.8 mL) was treated with Sc(OTf)$_3$ (18 mg, 0.037 mmol) and stirred at 60 °C under Ar for 24 h. Reaction was brought to RT, diluted with water (5 mL) and extracted with Et$_2$O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated to give the crude product (182 mg). Flash chromatography (5% Et$_2$O/Hexanes, 10 g SiO$_2$) gave the pure product (30 mg, 0.12 mmol, 32%).

^{1}H NMR (500 MHz, CDCl$_3$): δ 6.16 (s, 1H), 5.35 (s, 1H), 3.71 (d, J = 8.9 Hz, 1H), 2.04 (m, 1H), 1.74 (m, 4H), 1.66 (m, 1H), 1.42 (m, 2H), 1.3-1.1 (m, 7H), 1.21 (s, 3H), 1.06 (m, 2H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.5, 145.0, 119.5, 91.6, 45.3, 38.0, 33.1, 30.0, 29.6, 26.1, 25.6, 25.5, 25.4, 23.1, 23.0, 13.9; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2930, 1766, 1659, 1111; HRMS (EI, *m/z*) Calcd for $C_{16}H_{26}O_2$: 250.19328. Found: 250.19308. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.74; H, 10.49. Found: C, 76.14; H, 10.37.

4.5.5.6 (4R*, 5R*)-4-Butyl -4-methyl-3-methylene-5-(2-propyl)-dihydro-furan-2-one 9f

A solution of boronate **1b** (129 mg, 0.415 mmol) and isobutyraldehyde (52 mg, 0.72 mmol) in toluene (0.8 mL) was treated with Sc(OTf)$_3$ (20 mg, 0.041 mmol) and stirred at 60 °C under Ar for 18 h. Reaction was brought to RT, diluted with water (5 mL) and extracted with Et$_2$O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated to give the crude product (202 mg). Flash chromatography (5% Et$_2$O/Hexanes, 10 g SiO$_2$) gave the pure product (28 mg, 0.13 mmol, 32%).

^{1}H NMR (500 MHz, CDCl$_3$): δ 6.17 (s, 1H), 5.36 (s, 1H), 3.65 (d, J = 9.2 Hz, 1H), 2.04 (m, 1H), 1.44 (m, 2H), 1.3-1.1 (m, 4H), 1.22 (s, 3H), 1.06 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.5, 144.9, 120.0, 93.0, 45.3, 33.2, 28.5, 25.6, 23.1, 23.0, 20.4, 19.6, 13.9; IR (CH$_2$Cl$_2$ cast, cm^{-1}): 2960, 1767, 1659, 1111; HRMS (ES, *m/z*) Calcd for $C_{13}H_{22}O_2Na$: 233.151750. Found: 233.151637; Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.22; H, 10.56. Found: C, 73.60; H, 10.86.

4.5.5.7 (4R*, 5R*)-4-Butyl-5-isobutyl-4-methyl-3-methylene-dihydro-furan-2-one 9g

A solution of boronate **1b** (126 mg, 0.405 mmol) and isovaleraldehyde (54 mg, 0.62 mmol) in toluene (0.8 mL) was treated with Sc(OTf)$_3$ (22 mg, 0.045 mmol) and stirred at RT under Ar for 24 h. Reaction was diluted with water (5 mL) and extracted with Et$_2$O

(3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (88 mg). Flash chromatography (5% Et_2O/Hexanes, 10 g SiO_2) gave the pure product (48 mg, 0.21 mmol, 53%).

TLC (1% EtOAc/Toluene, $KMnO_4$): 0.20; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (s, 1H), 5.38 (s, 1H), 4.06 (dd, *J* = 10.9 Hz, 2.2 Hz, 1H), 1.86 (m, 1H), 1.59 (m, 1H), 1.4-1.0 (m, 7H), 1.13 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 144.3, 120.0, 86.0, 45.2, 37.3, 33.4, 25.6, 25.2, 23.5, 23.1, 21.6, 21.1, 13.9; IR (CH_2Cl_2 cast, cm^{-1}): 2957, 1769, 1661, 1111; HRMS (EI, *m/z*) Calcd for $C_{14}H_{24}O_2$: 224.17763. Found: 224.17738.

4.5.5.8 (4R*, 5R*)-4,5-Dibutyl-4-methyl-3-methylene-dihydro-furan-2-one 9h

A solution of boronate **1b** (126 mg, 0.406 mmol) and valeraldehyde (53 mg, 0.61 mmol) in toluene (0.8 mL) was treated with $Sc(OTf)_3$ (17 mg, 0.034 mmol) and stirred at RT under Ar for 24 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (160 mg). Flash chromatography (10% EtOAc/Hexanes, 10 g SiO_2) gave the pure product (47 mg, 0.21 mmol, 51%). A further 10 mg of product was obtained which was contaminated with trace amounts of valeraldehyde pinacol acetal. Overall yield: 57 mg, 0.25 mmol, 62%.

TLC (10% EtOAc/Hexanes, $KMnO_4$): 0.38; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (s, 1H), 5.38 (s, 1H), 3.98 (dd, *J* = 10.6 Hz, 2.9 Hz, 1H), 1.56 (m, 3H), 1.35 (m, 5H), 1.24 (m, 2H), 1.16 (m, 2H), 1.14 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 144.5, 120.0, 88.1, 45.2, 33.6, 28.8, 28.4, 25.6, 23.1, 22.5, 21.5, 13.9, 13.8; IR (CH_2Cl_2 cast, cm^{-1}): 3093, 2957, 1770, 1660, 1106; HRMS (EI, *m/z*) Calcd for $C_{14}H_{24}O_2$: 224.17763. Found: 224.17647; Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.94; H, 10.80. Found: C, 74.45; H, 10.87.

4.5.5.9 (4R*, 5S*)-5-Benzyloxymethyl-4-methyl-3-methylene-dihydro-furan-2-one 9i

A solution of boronate **1d** (67 mg, 0.29 mmol) and benzyloxyacetaldehyde (47 mg, 0.32 mmol) in toluene (0.6 mL) was treated with $Sc(OTf)_3$ (15 mg, 0.031 mmol) and stirred at RT under Ar for 25 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (73 mg). Flash chromatography (10% Et_2O/Hexanes, 5 g SiO_2) gave the pure product (22 mg, 0.095 mmol, 33%).

TLC (25% Et_2O/Hexanes, $KMnO_4$): 0.10; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.25 (m, 3H), 6.16 (d, $J = 3.2$ Hz, 1H), 5.45 (d, $J = 2.8$ Hz, 1H), 4.64 (m, 1H), 4.51 (AB, $J = 12.0$ Hz, 1H), 4.49 (AB, $J = 12.3$ Hz, 1H), 3.63 (dq, $J = 10.8$ Hz, 4.2 Hz, 2H), 3.59 (m, 1H), 1.24 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 140.4, 137.6, 128.4, 127.7, 127.4, 119.2, 79.1, 73.6, 68.7, 36.4, 13.1; IR (CH_2Cl_2 cast, cm^{-1}): 3030, 1764, 1663, 1121, 731, 698; HRMS (EI, *m/z*) Calcd for $C_{14}H_{16}O_3$: 232.10994. Found: 232.1010; Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.96. Found: C, 72.01; H, 6.87.

4.5.6 Catalysed allylborations with aliphatic aldehydes – Second Generation method

4.5.6.1 (4R, 5S*)-4-Ethyl-4-methyl-3-methylene-5-phenethyl-dihydro-furan-2-one 9a*

A solution of boronate **1a** (100 mg, 0.354 mmol) and hydrocinnamaldehyde (46 mg, 0.34 mmol) in toluene (0.7 mL) was treated with $Sc(OTf)_3$ (20 mg, 0.041 mmol) and phenylboronic acid (44 mg, 0.36 mmol). The resulting mixture was stirred at RT under Ar for 18 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (138 mg). Flash chromatography (25% Et_2O/Hexanes, 16 g SiO_2) gave the pure product (69 mg, 0.28 mmol, 82%). The spectral characteristics for this compound were described in Section 4.5.5.1.

4.5.6.2 (4R, 5R*)-5-Benzyloxymethyl-4-ethyl-4-methyl-3-methylene-dihydro-furan-2-one 9b*

A solution of boronate **1a** (86 mg, 0.30 mmol) and benzyloxyacetaldehyde (45 mg, 0.30 mmol) in toluene (0.6 mL) was treated with $Sc(OTf)_3$ (18 mg, 0.037 mmol) and phenylboronic acid (40 mg, 0.32 mmol). The resulting mixture was stirred at RT under Ar for 19 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (134 mg). Flash chromatography (25% Et_2O/Hexanes, 6 g SiO_2) gave the pure product (42 mg, 0.16 mmol, 54%). The spectral characteristics for this compound were described in Section 4.5.5.2.

4.5.6.3 *(4R*, 5S*)-4-Ethyl-4-methyl-3-methylene-5-(2-methylpropyl)-dihydro-furan-2-one 9c*

A solution of boronate **1a** (104 mg, 0.37 mmol) and isovaleraldehyde (32 mg, 0.38 mmol) in toluene (0.7 mL) was treated with $Sc(OTf)_3$ (18 mg, 0.037 mmol) and stirred at RT under Ar for 12 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (122 mg). Flash chromatography (50% CH_2Cl_2/Hexanes, 6 g SiO_2) gave the pure product (48 mg, 0.24 mmol, 66%). The spectral characteristics for this compound were described in Section 4.5.5.3.

4.5.6.4 *(4R*, 5S*)-5-Benzyloxymethyl-4-methyl-3-methylene-dihydro-furan-2-one 9i*

A solution of boronate **1d** (70 mg, 0.30 mmol) and benzyloxyacetaldehyde (50 mg, 0.33 mmol) in toluene (0.6 mL) was treated with $Sc(OTf)_3$ (15 mg, 0.037 mmol) and phenylboronic acid (46 mg, 0.38 mmol). The resulting mixture was stirred at RT under Ar for 25 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (96 mg). Flash chromatography (25% Et_2O/Hexanes, 6 g SiO_2) gave the pure product (42 mg, 0.18 mmol, 60%). The spectral characteristics for this compound were described in Section 4.5.5.9.

4.5.7 Enantioselective catalysed reactions

4.5.7.1 *Enantioselective allylboration with 8-phenylmenthol boronate 14 under $Sc(OTf)_3$ catalysis*

Boronate **14** (55 mg, 0.12 mmol) and decanal (29 mg, 0.18 mmol) in toluene (0.25 mL) was treated with $Sc(OTf)_3$ (5 mg, 0.01 mmol) and stirred at RT under Ar. After 24 h, the mixture was diluted with CH_2Cl_2 (5 mL), treated with a spatula tip of pTSA, and stirred for 3 h. The reaction was quenched with $NaHCO_{3(aq)}$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined ether layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (34 mg), which was purified by flash chromatography (1% EtOAc/Toluene, 8 g silica) to give the enantioenriched product **16** (9 mg, 29%). Chiral HPLC analysis (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min) showed that the enantiomeric excess of the product was 10% for the (*R*)-enantiomer.

4.5.7.2 Enantioselective allylboration with 8-phenylmenthol boronate 14 under $Cu(OTf)_2$ catalysis

This reaction was performed following the procedure outlined in Section 4.5.7.1, using boronate **14** (59 mg, 0.13 mmol), decanal (30 mg, 0.18 mmol), and $Cu(OTf)_2$ (5 mg, 0.01 mmol). Work-up and purification gave lactone **16** in 93% yield and with a 71% ee for the (*S*)-enantiomer.

4.5.7.3 Enantioselective allylboration with 8-phenylmenthol boronate 14 under $Yb(OTf)_3$ catalysis

This reaction was performed following the procedure outlined in Section 4.5.7.1, using boronate **14** (63 mg, 0.14 mmol), decanal (32 mg, 0.20 mmol), and $Yb(OTf)_3$ (9 mg, 0.01 mmol). Work-up and purification gave lactone **16** in 30% yield and with a 31% ee for the (*S*)-enantiomer.

4.5.7.4 Enantioselective allylboration with boronate 15 under $Sc(OTf)_3$ catalysis

Boronate **15** (120 mg, 0.30 mmol) and decanal (70 mg, 0.45 mmol) in toluene (0.6 mL) was treated with $Sc(OTf)_3$ (19 mg, 0.04 mmol) and stirred at RT under Ar. After 24 h, the mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined ether layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (145 mg), which was purified by flash chromatography (25% Et_2O/Hexanes, 7 g silica) to give the enantioenriched product **16** (40 mg, 53%). Chiral HPLC analysis (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min) showed that the enantiomeric excess of the product was 3% for the (*R*)-enantiomer.

4.5.7.5 Enantioselective allylboration with boronate 15 under $Cu(OTf)_2$ catalysis

This reaction was performed following the procedure outlined in Section 4.5.7.4, using boronate **15** (119 mg, 0.30 mmol), decanal (73 mg, 0.46 mmol), and $Cu(OTf)_2$ (12 mg, 0.33 mmol). Work-up and purification gave lactone **16** in 31% yield and with a 13% ee for the (*R*)-enantiomer.

4.5.7.6 Enantioselective allylboration with boronate 15 under $Yb(OTf)_3$ catalysis

This reaction was performed following the procedure outlined in Section 4.5.7.4, using boronate **15** (132 mg, 0.334 mmol), decanal (78 mg, 0.50 mmol), and $Yb(OTf)_3$ (19 mg, 0.30 mmol). Work-up and purification gave lactone **16** in 37% yield and with a 21% ee for (*R*)-enantiomer.

4.5.7.7 Enantioselective allylboration with Bis(oxazolinyl)pyridine-scandium triflate catalyst

This procedure was based on the one published by Evans and co-workers.[14] A mixture of $Sc(OTf)_3$ (22 mg, 0.045 mmol) and (*S*)-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine (23 mg, 0.063 mmol) were stirred in CH_2Cl_2 (1.5 mL) under Ar for 3 h, after which time it was treated with boronate **1a** (133 mg, 0.47 mmol) and decanal (72 mg, 0.46 mmol). A small aliquot was removed after 16 h and ^1H NMR analysis of a small aliquot showed that the reaction was ~20% complete. After heating at 40 °C for 24 h, toluene (1 mL) was added to the mixture and the reaction was heated at 110 °C for an additional 24 h. Finally, water (1 mL) was added and the mixture was heated at 110 °C for 48 h. The mixture brought to RT, diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined ether layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product (100 mg), which was purified by flash chromatography (10% Et_2O/Hexanes, 7 g silica) to give the enantioenriched product (17 mg, 0.064 mmol, 14%). Chiral HPLC analysis (CHIRALPAK AD-RH, 50% isopropanol/water, 0.3 mL/min) showed that the enantiomeric excess of the product was 19%.

4.6 References

(1) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289-4292.

(2) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis-Stuttgart* **2000**, 990-998.

(3) Batey, R. A.; Quach, T. D.; Shen, M.; Thadani, A. N.; Smil, D. V.; Li, S. W.; MacKay, D. B. *Pure Appl. Chem.* **2002**, *74*, 43-55.

(4) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415.

(5) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331-8336.

(6) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868-1874.

(7) Ooi, T.; Maruoka, K. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2001**, pp 1-32.

(8) Kobayashi, S. *Synlett* **1994**, 689-701.

(9) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587.

(10) Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077-1078.

(11) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. I. *Synlett* **1996**, 557-&.

(12) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758-3759.

(13) Evans, D. A.; Masse, C. E.; Wu, J. *Org Lett* **2002**, *4*, 3375-3378.

(14) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095-12096.

(15) Zhu, N.; Hall, D. G. *Unpublished Results.*

(16) Clapham, G.; Shipman, M. *Tetrahedron Lett.* **1999**, *40*, 5639-5642.

(17) Clapham, G.; Shipman, M. *Tetrahedron* **2000**, *56*, 1127-1134.

(18) Denmark, S. E.; Fu, J. P. *Chem. Commun.* **2003**, 167-170.

(19) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405-13407.

(20) Kennedy, J. W. J.; Hall, D. G. *Synlett* **2002**, 477-479.

(21) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183-7189.

(22) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, **2001**, pp 299-401.

(23) Rodriguez, A.; Miller, D. D.; Jackson, R. F. W. *Org. Biomol. Chem.* **2003**, *1*, 973-977.

(24) Hoffmann, R. W.; Schlapbach, A. *Tetrahedron* **1992**, *48*, 1959-1968.

PART II

Chapter 5

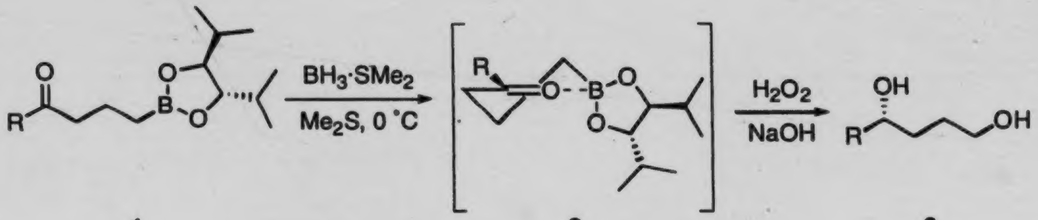
Self-Activation and Long-range Stereochemical Induction in 2-Boronacrylanilides

5.1 Introduction

Chiral boronic acids have proven themselves to be useful catalysts in many enantioselective reactions.[1] Unfortunately, there are many transformations in synthetic chemistry for which an effective chiral catalyst is not yet known. In these cases, a stereoselective reaction may be realized via use of a stoichiometric chiral auxiliary. Despite the large number of chiral auxiliaries already developed,[2] a single, all-purpose auxiliary which is effective for all transformations has yet to be discovered.

An ideal auxiliary would be easily installed on the substrate, provide high levels of stereoinduction in the subsequent reaction, and then be readily cleaved from the product. An ongoing research program in our research group is the development of novel applications of organoboronic acids in asymmetric synthesis. As a part of this program, we set out to design a new boron-based chiral auxiliary. Our goal was to develop an auxiliary that would not only act as a chiral directing group, but would also take advantage of the inherent Lewis acidity of boron to accelerate the reaction.

The idea of using a boronic acid auxiliary that activates as well as directs is not new. Molander and Bobbitt validated this concept by showing that the internal boronic ester in substrate **1** could act as a chiral auxiliary for the reduction of a remote ketone (Table 5-1).[3] This case of 1,7-stereoinduction is thought to proceed via formation of the 6-membered chelate **2** prior to reduction. After reduction, the auxiliary is conveniently removed by oxidation to give the diol **3**. However, despite the remarkable success seen in this and related reductions,[4-6] this methodology suffers from the fact that the chiral boronate is not conveniently installed.

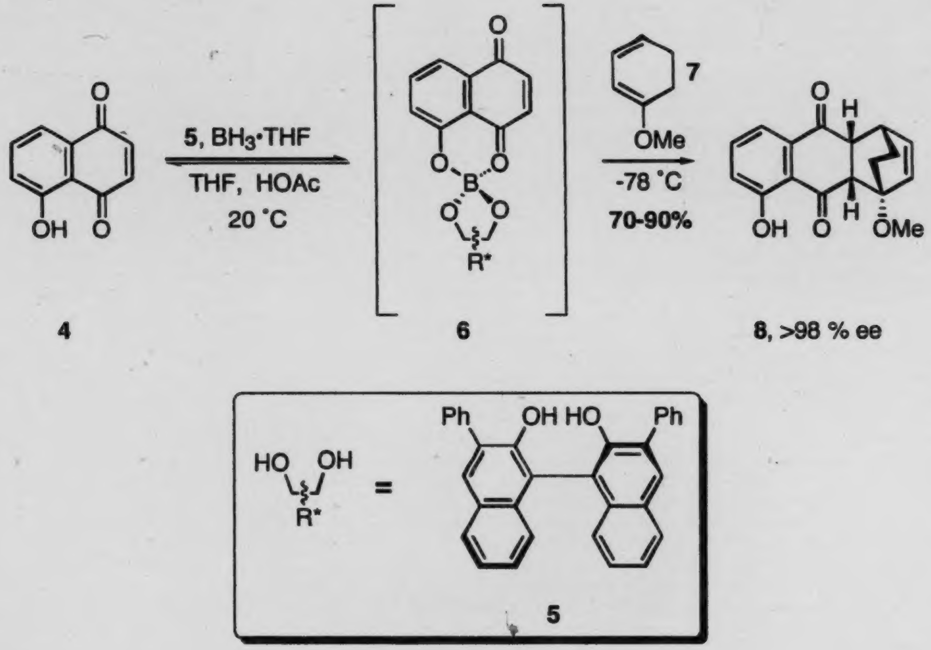


1 2 3

Entry	Product	R	Yield (%)	ee (%)
1	**3a**	CH_3	83	85
2	**3b**	C_5H_{11}	87	92
3	**3c**	(c)-C_6H_{11}	85	>98
4	**3d**	C_6H_5	95	97
5	**3e**	$CH_3O_2C(CH_2)_4$	95	>96

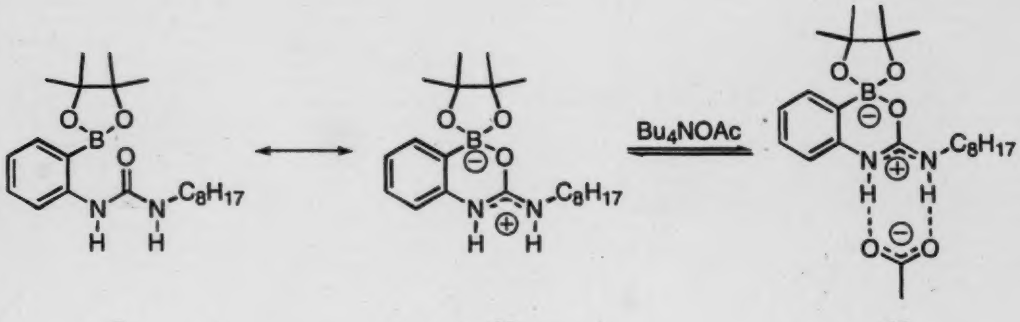
Table 5-1. Stereoselective reductions with a boron-containing chiral auxiliary.

In another example, boronic esters can promote Diels-Alder reactions of jugulone **4** (Scheme 5-1).[7] Addition of **4** to a stoichiometric amount of a chiral boronic ester, generated *in situ* from borane, acetic acid, and the binaphthol auxiliary **5**, forms the transient chelate **6**, where the coordination of the boron to the lower carbonyl is anchored by the free hydroxyl group. The C_2-symmetrical auxiliary then shields the top face of the dienophile in **6**, allowing for selective approach of diene **7** to the bottom face, yielding cycloadduct **8** in good yield and excellent selectivity. The authors note that the reaction between **4** and cyclohexadiene **7** is incomplete, even after 2 days, in the absence of the chelating group. This result highlights the remarkable rate acceleration observed with this auxiliary. Unfortunately, because the chelate **6** has very specific structural requirements (*i.e.*, a rigidly held β-hydroxyketone), reactions based on this methodology have so far been limited to the use of jugulone and its analogues as the dienophile.[8-10]



Scheme 5-1

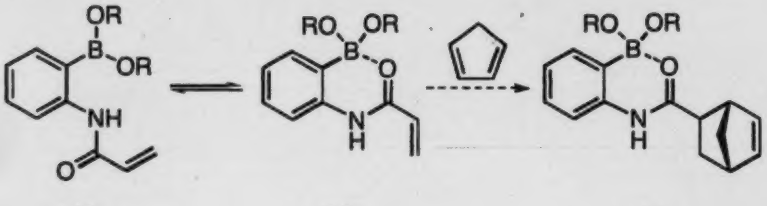
However, we wondered if an alternative, more versatile scaffold could be found that would allow this Diels-Alder chemistry to be extended to other dienophiles. Our interest was piqued by reports that boron-containing aromatic ureas **9** were self-activating systems (Scheme 5-2).[11,12] These compounds do not really exist in the form of **9** but rather as the zwitterionic structure **10**, where the boron acts as an internal Lewis acid and coordinates to the urea carbonyl. This chelation polarizes the urea and allows for 20-30 fold increase in the binding of acetate anions (via complex **11**) compared to analogues where this chelation is not possible.



9 **10** **11**

Scheme 5-2

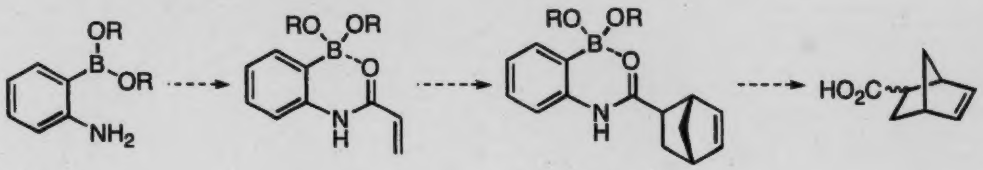
Although this system was studied in the search for synthetic anion receptors, we believed that it could be adapted to apply the self-activation effect to stereoselective synthetic chemistry. Specifically, we thought that the *ortho*-boronic acid substituent could activate the dienophile **12** via formation of the chelate **13** (Scheme 5-3). Here, the carbonyl of the acrylamide could be activated via a 6-membered chelate **13**. Hopefully, this activation would be sufficient to cause a significant increase in the rate of the reaction. We also felt that chiral ligands on the boron might be able to influence the stereochemistry of the cycloadducts. The stereochemistry of these ligands could be transmitted via the boron, much in the same way as in the selective reactions with jugulones (see above).



12 **13** **14**

Scheme 5-3

The main advantage of this system is that it could potentially fulfill all of the requirements for an ideal auxiliary (Scheme 5-4). The auxiliary 2-aminoboronate **15** can be easily attached to an acrylate unit by amide coupling procedures to give dienophile **13**. Similarly, the stereo-enriched cycloadducts **16** could be liberated from the product **14** by standard amide cleavage protocols. In this regard, the anilide system has a distinct advantage in that aromatic amides are generally easier to cleave than their saturated analogues. The rest of this chapter summarizes our evaluation of the ability of this auxiliary to provide rate acceleration and stereoinduction in [4+2] cycloaddition reactions. Results from this study have already been published.[13,14]



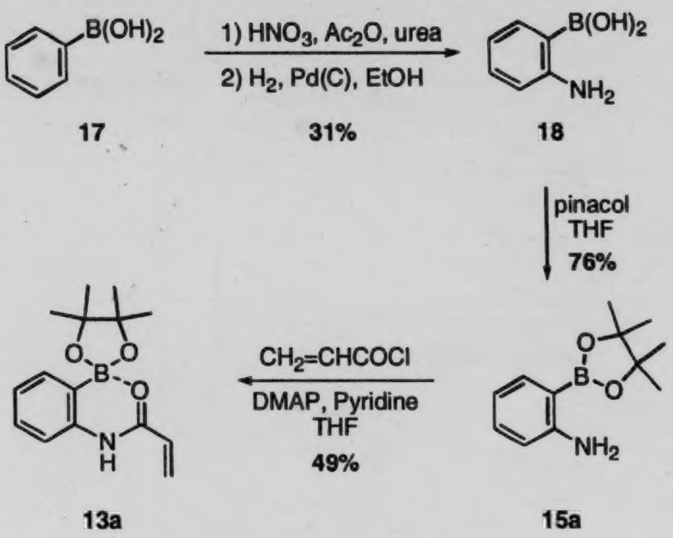
15 **13** **14** **16**

Scheme 5-4

5.2 Results

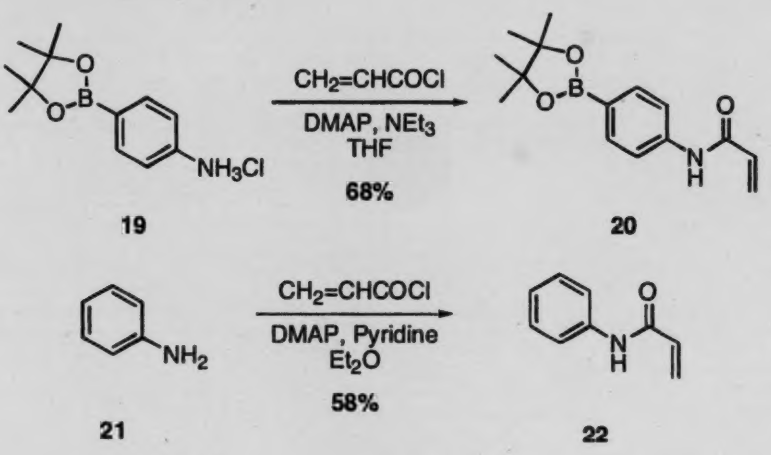
5.2.1 Rate acceleration with 2-boronacrylanilides.

The first step in this project was to determine whether the *ortho*-boronic ester in **13** was indeed capable of activating the dienophile. We used the pinacol boronate **13a** for this part of the study because these esters were easy to prepare and handle. Thus, dienophile **13a** was easily prepared in four steps from phenylboronic acid (Scheme 5-5). Nitration of phenylboronic acid[15] followed by hydrogenation of the isolated *ortho* isomer[16] yielded aminoboronic acid **18**. Esterification of the boronic acid with pinacol furnished aminoboronate **15a**, which was then reacted with acryloyl chloride to provide acrylanilide **13a**.



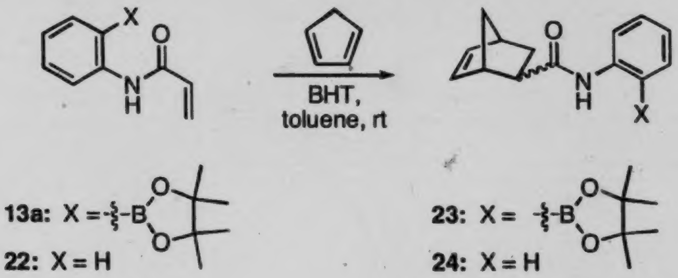
Scheme 5-5

In addition, two other dienophiles were prepared to act as control compounds (Scheme 5-6). The *para*-boronate **20** was made in a similar manner to **13a** from the commercial ammonium salt **19**, and the unsubstituted acrylanilide **22** was accessed from aniline **21** following a published procedure.[17]



Scheme 5-6

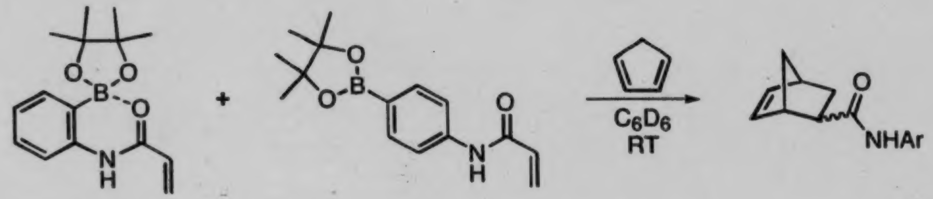
To probe the effect of the boronate substituent, the [4+2] cycloadditions of dienophiles **13a** and **22** with cyclopentadiene were studied by measuring the ratio of starting material to cycloadducts by ^{1}H NMR analysis on crude reaction mixtures. Although dienophile **13a** is more sterically hindered, the data show that it reacts noticeably faster than **22** and with increased *endo*/*exo* selectivity in the resulting adducts **23** and **24** (Table 5-2). These results are consistent with a small self-activation effect by internal coordination between the boronic ester and the carbonyl group in dienophile **13a**.



Time (h)	22		13a	
	s.m. : adduct	*endo* : *exo*	s.m. : adduct	*endo* : *exo*
1	*No reaction*		2.7 : 1	3.8 : 1
6	1 : 0.4	2.5 : 1	1.2 : 1	3.8 : 1
48	1: 5	2.8 : 1	1 : 13	4.3 : 1

Table 5-2. Relative speed and *endo* : *exo* ratios from Diels-Alder reactions of **23** and **24**. Ratios of starting materials (s.m.) and cycloadducts were measured by ^{1}H NMR on the crude reaction mixtures.

To rule out the possibility that the activation may be due to the electron-withdrawing effect of the boronate group on the reactivity of the acrylamide dienophile, a competitive kinetic experiment was performed whereby **13a** and the corresponding *para*-substituted isomer **20** were allowed to react simultaneously with excess cyclopentadiene (Figure 5-1). The proportion of components in the reaction mixture showed the faster consumption and conversion to cycloadducts of **13a** compared to **22**. This result further confirms that self-activation by internal coordination is operative in the case of *ortho*-substituted dienophile **13a**.



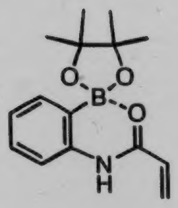
13a

20

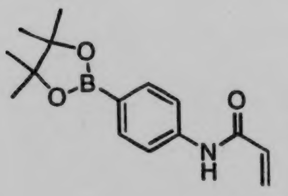
	para s.m.	:	*ortho* s.m. :	:	*para* adducts. :	:	*ortho* adducts. (%)
Start point	55	:	45	:	0	:	0
After 17 d	43	:	11	:	10	:	36

Figure 5-1. Relative percentages of components as measured by signal integration on ^{1}H NMR spectra of the crude reaction mixtures. (s.m. = starting material)

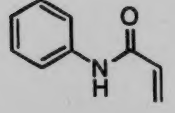
We attempted to find spectroscopic evidence for the proposed intramolecular coordination in structure **13a** (Table 5-3). The carbonyl stretch in the infra-red for the *ortho*-boronoacrylanilide **13a** is significantly red-shifted by ~20 cm^{-1} compared to the same stretch in the *para*-isomer **20** and the unsubstituted aniline **22**, suggesting that this coordination occurs in the solid-state. This coordination is also clearly evident by X-ray crystallography (see next section). However, ^{11}B NMR spectra for the two boronacrylanilides **13a** and **20** both gave signals at similar chemical shifts typical of a trigonal boronic ester. Nevertheless, the rate enhancement observed in the Diels-Alder studies presented above is a real effect, and strongly points to such a coordination. We currently believe that this coordination is either very weak in the solution state, or that it occurs as part of a dynamic process. Interestingly, we are not the first group to have trouble finding direct evidence for a boron-carbonyl coordination in a situation where reactivity patterns suggest that it might exist.[3,4]



13a



20



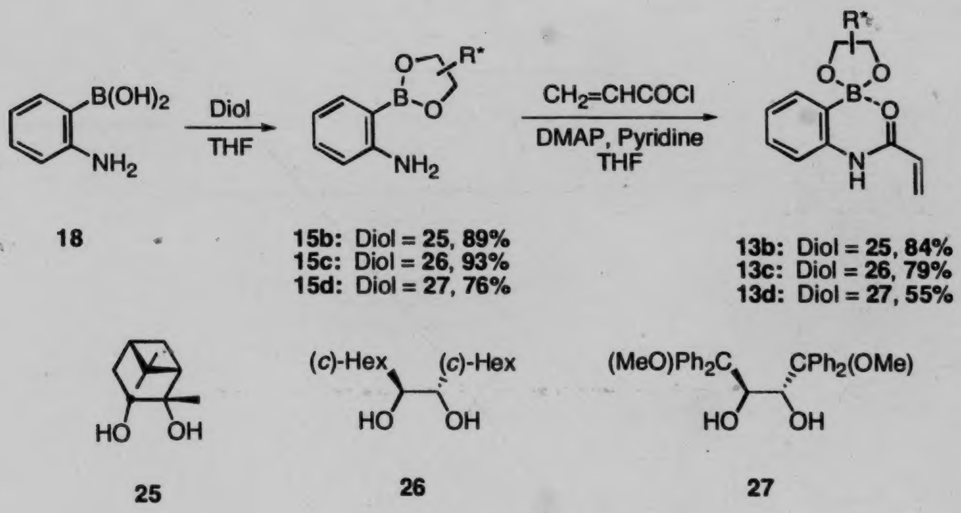
22

Spectroscopic Technique	*ortho*-**13a**	*para*- **20**	Acrylanilide **22**
IR ($\nu_{C=O}$)	1646 cm^{-1}	1667 cm^{-1}	1668 cm^{-1}
^{11}B NMR	30.1 ppm	30.8 ppm	-

Table 5-3. Spectroscopic evidence for and against internal coordination in boronoacrylanilide **13a**. Infrared spectrum taken as a solid film. ^{11}B NMR spectrum recorded in C_6D_6 at 64 MHz.

5.2.2 Remote stereoinduction with 2-boronacrylanilides.

We next turned our attention towards evaluating the appealing possibility that internal coordination could serve at communicating stereochemistry in a long-range fashion. As can be seen in a recent review on the subject, there are very few examples of remote stereoinduction beyond a 1,7-relationship between the inducing center and the reactive one.[18] In the present case, 1,8-stereoinduction (as measured between the closest carbon atoms in the dienophilic olefin and the chiral boronate substituent in the absence of coordination in **13a**) could be transmitted via internal carbonyl coordination to the boron atom. In this way, the resulting tetrahedral boronate, rendered stereogenic at boron, would involve a temporary situation of 1,4-stereoinduction. We imagined that known diol boronate auxiliaries such as pinanediol **25**, 1,2-dicyclohexyl-1,2-ethanediol **26**,[19] and 1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol **27** could be useful in this regard.[20] Thus, the chiral dienophiles **13b-d** (Scheme 5-7) were assembled from 2-aminophenylboronic acid **18** and the enantiopure diols in a manner analogous to **13a**.



18

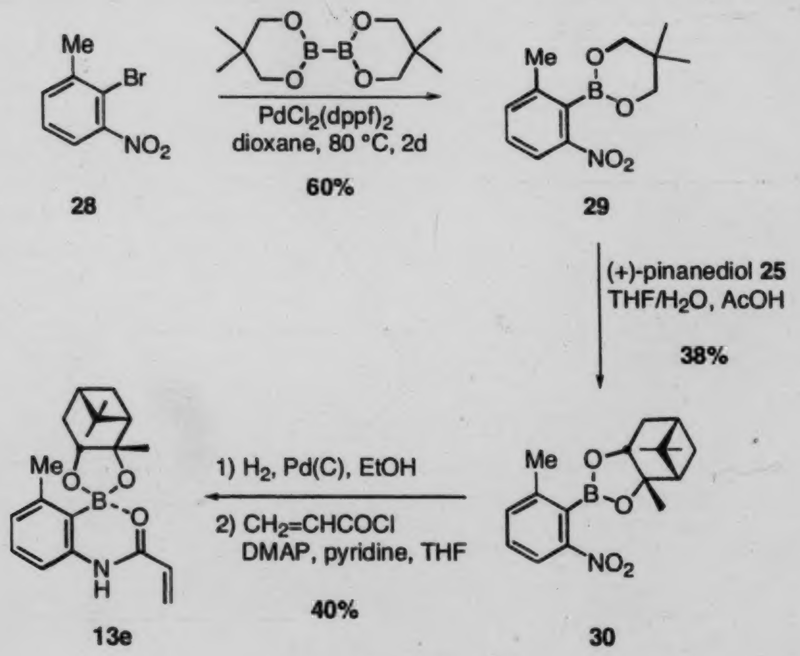
15b: Diol = **25, 89%**
15c: Diol = **26, 93%**
15d: Diol = **27, 76%**

13b: Diol = **25, 84%**
13c: Diol = **26, 79%**
13d: Diol = **27, 55%**

25 **26** **27**

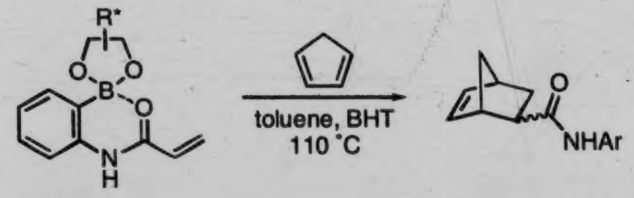
Scheme 5-7

The novel, tolyl analogue of **13b**, pinanediol boronate **31**, was synthesized starting with the palladium-catalyzed borylation of aryl bromide **28**,[21,22] followed by transesterification of the resulting boronic ester **29** with (+)-pinanediol **25** to give **30** (Scheme 5-8). The latter intermediate was hydrogenated and treated with acryloyl chloride to provide acrylamide dienophile **31** in moderate yield.



Scheme 5-8

These chiral dienophiles were then allowed to react with cyclopentadiene and the diastereoselectivities of the reactions were measured by ^{1}H NMR of the resulting cycloadducts **23** (Table 5-4). Unfortunately, the level of 1,8-stereoinduction observed in these compounds was quite low, and the highest value of 28% diastereomeric excess originated from the *exo* cycloadduct of dienophile **13c**. The selectivities observed in the *endo* cycloadducts were uniformly poor. The higher selectivity of the *exo* addition pathway in the approach of cyclopentadiene to the S-*cis* acrylamide is consistent with the higher steric demand of the methylene unit compared to the planar diene moiety.



13

23

Entry	Dienophile	Yield (%)	*endo* : *exo*[a]	de_{endo} (%)[a]	de_{exo} (%)[a]
1	**13b**	94	2.0 : 1	8	6
2	**13e**	56	1.5 : 1	5	9
3	**13c**	46	1.4 : 1	5	18
4[b]	**13c**	72	3.7 : 1	0	28
5	**13d**	(100)[c]	1.7 :1	6	22
6[d]	**13d**	(73)[c]	1.9 : 1	9	18
7[e]	**13d**	(85)[c]	2.4 : 1	(-6)[f]	22

Table 5-4. Level of remote 1,8-stereoinduction in the Diels-Alder reaction between **13b-d** and cyclopentadiene. [a] Ratios of cycloadducts were measured from representative signals by ^{1}H NMR on the crude reaction mixtures. [b] Reaction performed at room temperature in CH_2Cl_2 for 3 days. [c] Yields in brackets are percent conversions determined from ^{1}H NMR of the crude mixture. [d] Reaction performed at room temperature. [e] Reaction performed at room temperature in CH_2Cl_2. [f] Preference is for the opposite isomer compared to the reaction in toluene.

An inspection of the X-ray crystal structure of dienophile **13b**, displayed as an ORTEP diagram in Figure 5-2, may provide some insight towards explaining these results. Although the ^{11}B NMR data did not show evidence for strong coordination (see previous section), the boronic ester is firmly coordinated to the acrylanilide carbonyl in the solid state structure to form a tetrahedral boronate. Similar B-O coordination has previously been observed in an α-acetamidomethaneboronate.[23] Unfortunately, the boronate substituents in **13b** appear to be too distant from the dienophile to allow effective transmission of stereochemistry. Acrylanilide **13b** provided diastereoselectivities below 10% in the cycloaddition study, and Figure 5-2 shows that the bulkiest part of the pinanedioxy group (the gem-dimethyl bridge) is oriented away from the reaction center. This arrangement leaves only the C3 hydrogen and the C2 methyl as discriminating groups for effecting diastereofacial selectivity. Interestingly, this observation suggested that the replacement of hydrogen for a bulkier group at C16 of the aromatic ring (*ortho* to the boronic ester) could induce a preference for a different boronate configuration. Such an arrangement could place the bulk of the pinane group *syn* to the acrylamide moiety, or at least tip over the gem-dimethyl bridge closer to the reaction center to potentially allow a more effective transfer of chirality. Unfortunately, the experimental results from the Diels-Alder reaction of **13e** clearly showed that this additional methyl group is not sufficient to allow for high selectivities with these substrates.

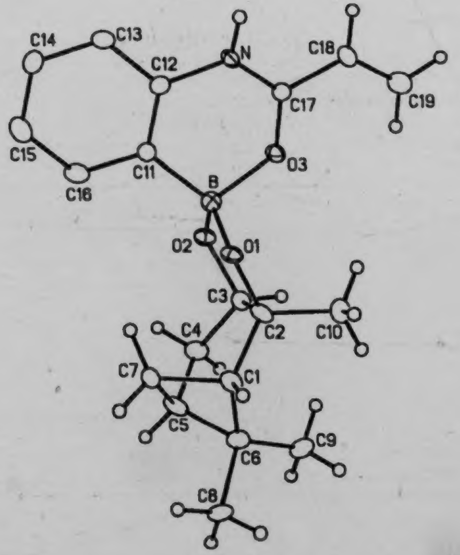
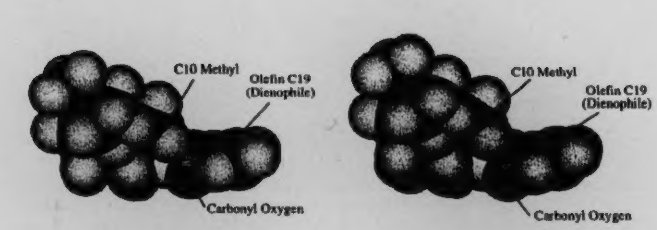
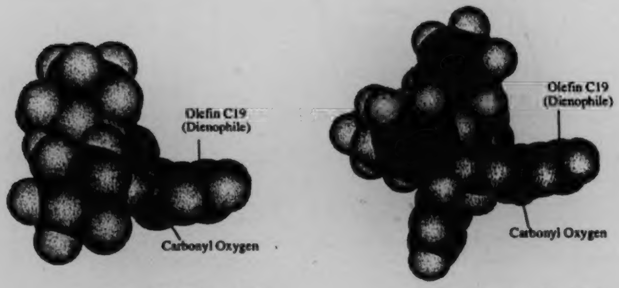


Figure 5-2. ORTEP display of the X-ray structure of acrylanilide **13b**.

In order to probe the steric effect of the boronate ester on the diastereoselectivity of the Diels-Alder reaction, qualitative molecular modeling analysis of boronates **13b** and **13e** was carried out, based on the crystal structure of **13b**. The resulting models showed that although the added methyl group in **13e** does indeed tip the pinane-unit closer to the reaction centre, the effect is very small and the chiral auxiliary remains quite remote from the acrylamide (Figure 5-3). However, molecular modeling analysis of **13c** and **13d** supported the experimental results showing that these two chiral boronates were the most efficient ones at providing steric discrimination between the two faces of the dienophile component, with diastereomeric excesses that were notably higher than those obtained with boronates **13b** and **13e**. The qualitative models of boronates **13c** and **13d** show that the chiral auxiliaries are significantly closer to the acrylamide unit than the pinanediol moiety in boronates **13b** and **13e** (Figure 5-3). However, as with the other two chiral boronates, the auxiliaries are still too far removed from the reaction centre to induce high levels of selectivity.



Acrylanilide **13b** Acrylanilide **13e**

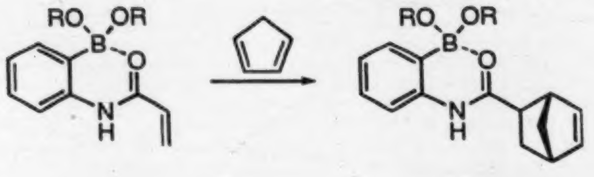


Acrylanilide **13c** Acrylanilide **13d**

Figure 5-3. Molecular models of acrylanilides **13b-e** with atom numbering as per Figure 5-2.

5.3 Conclusion

This work shows that 2-aminophenyl boronic esters can be used as chiral auxiliaries. In this specific case, we demonstrated that the non-activated dialkoxyboronic ester operates as a weak, internal Lewis acid and activates an acrylate unit towards cycloaddition reactions (Scheme 5-9). This moderate activation was clearly shown to be a result of the internal coordination between the carbonyl and the boron. This coordination was also shown to exist in the solid state by X-ray crystallography. We further showed that chiral boronates can induce selectivity in these cycloadditions in an example of 1,8-stereoinduction transmitted through a putative tetrahedral stereogenic boronate complex. Even if the observed diastereoselectivities were quite low, the fact that an auxiliary which is so remote from the reaction centre can have an effect at all is quite remarkable. Although the current system would need to be redesigned in order to find general applicability, these results validate the concept of internal activation and may pave the way to significant advances in the future.



13 **14**

- Internal activation of carbonyl achieved
- Accelerated rate versus unactivated substrate and long-range stereoinduction observed.
- Both effects quite modest.

Scheme 5-9

5.4 Experimental

5.4.1 General

The methods described in Section 2.3.1 (page 34) also apply here, with the following additions. 2-Nitrophenylboronic acid and 4-aminophenylboronic acid hydrochloride pinacol ester were purchased from Combi-Blocks Inc. and used as received. 1,4-Dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol was prepared according to the literature procedure.[20] All other chemicals were purchased from either the Aldrich Chemical Company or Caledon Chemicals and used as received. Starting structures used in the molecular modeling calculations were drawn in ChemDraw Ultra (Version 7.0.1) using the X-ray structure of compound **13b** as a guide. The structures were then imported into Chem3D Pro (version 5) and minimized using the MM2 force field. X-ray crystallographic data for **13b** have been deposited to the Cambridge Crystallographic Data Centre (file number: CCDC 166880).

5.4.2 Preparation of aminoarylboronic acids

5.4.2.1 2-Aminophenylboronic acid, pinacol ester 15a

A solution of 2-aminoboronic acid **18** (1.68 g, 12.3 mmol) and pinacol (1.50 g, 12.6 mmol) in THF (120 mL) was stirred under N_2 overnight. The solvent was removed and the residue was purified by flash chromatography (20% EtOAc/Toluene, 160 g SiO_2) to give the product as a white solid (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 7.4 Hz, 1.4 Hz, 1H), 7.26 (m, 1H), 6.72 (m, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 4.76 (br s, 2H), 1.39 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 136.3, 132.6, 116.5, 114.6, 110.2 (broad), 83.3, 24.6; IR (microscope): 3488, 3384, 2977, 1606, 1354 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{12}H_{18}O_2N^{11}B$: 219.14307, found 219.14317.

5.4.2.2 2-Aminophenylboronic acid, (+)-pinanediol ester 15b

As per **15a**, with 2-aminoboronic acid **18** (585 mg, 4.27 mmol) and (+)-pinanediol **25** (811 mg, 4.76 mmol) in THF (50 mL). Flash chromatography (20% EtOAc/Toluene, 40 g silica) gave the product as a white solid (1.03 g, 3.81 mmol, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 8.2 Hz, 1H), 6.68 (t, *J* = 7.3, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 4.69 (br s, 2H), 4.44 (dd, *J* = 8.6 Hz, 1.1 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 2.14 (m, 1H), 1.99 (m, 1H), 1.94 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 136.7, 132.5, 116.7, 114.6, 110.4, 85.8, 77.7, 51.3, 39.4, 38.0, 35.5, 28.7, 27.0, 26.4, 23.9; IR (CH_2Cl_2 cast): 3487, 3388, 1605 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{16}H_{22}O_2N^{11}B$ 271.17435, found 271.17466.

5.4.2.3 2-Aminophenylboronic acid, (-)-1,2-dicyclohexyl-1,2-ethanediol ester 15c

As per **15a**, with 2-aminoboronic acid **18** (152 mg, 1.11 mmol), (-)-1,2-dicyclohexyl-1,2-ethanediol **26** (282 mg, 1.25 mmol) and THF (10 mL). Flash chromatography (10% Et_2O/Hexane, 27 g silica, pre-absorption) gave the product as a colourless oil (340 mg, 1.04 mmol, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.5 Hz, 1.6 Hz, 1H), 7.23 (m, 1H), 6.88 (dt, *J* = 7.2 Hz, 0.8 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.65 (br s, 2H), 4.00 (d, *J* = 5.3 Hz, 2H), 2.0-1.6 (m, 9H), 1.42 (m, 2H), 1.3-0.8 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 136.9, 132.7, 116.9, 114.8, 83.6, 43.0, 28.5, 27.5, 26.4, 26.0, 25.8; IR (CH_2Cl_2 cast) 3488, 3389, 1609, 754 cm^{-1}; HRMS (EI, *m/z*) Calcd for $C_{20}H_{30}O_2N_{11}B$ 327.23697, found 327.23704.

5.4.2.4 2-Aminophenylboronic acid, (2R, 3R)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol ester 15d

2-Aminoboronic acid **18** (133 mg, 0.970 mmol) and (2*R*, 3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol **27** (438 mg, 0.964 mmol) were refluxed in THF (5 mL) in the presence of 4 Å molecular sieves under argon for 2 days. The mixture was then filtered through silica and concentrated to give the crude product. Flash chromatography (10% Acetone/Hexanes, 25 g SiO_2) gave the product as a colourless oil (408 mg, 0.735 mmol, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.20 (m, 21H), 7.07 (dt, *J* = 8.2 Hz, 1.5 Hz, 1H), 6.47 (t, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 8.1 Hz, 1H), 5.45 (s, 2H), 4.15 (br s, 2H), 2.98 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8, 141.5, 141.1, 136.6, 132.3, 129.5, 128.3, 127.8, 127.5, 127.4, 127.2, 116.5, 114.4, 83.5, 78.0, 52.0; ^{11}B (64 MHz, $CDCl_3$): δ 30.6; IR (CH_2Cl_2 cast): 3490, 3392, 3056, 2832, 1617, 1605, 1353, 757, 701 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{36}H_{34}O_4N^{11}B$: 555.25812, found 555.23687.

5.4.2.5 2-Nitro-6-methyphenylboronic acid, neopentylglycol ester 29

A slurry of bis(neopentyl glycolato)diboron (677 mg, 3.00 mmol), $PdCl_2(dppf)_2$ (56 mg, 0.069 mmol), dppf (39 mg, 0.071 mmol) and KOAc (758 mg, 7.72 mmol) in anhydrous dioxane (15 mL) under argon was treated with 3-nitro-2-bromotoluene **28** (553 mg, 2.56 mmol) and heated at 80 °C for 2 d. The resulting dark mixture was then diluted with toluene (50 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the crude product. Kugelrohr distillation (250 °C, 0.1 torr) gave the product as a brown oil that solidified over time (385 mg, 1.54 mmol, 60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 8.3 Hz, 0.5 Hz, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 3.81 (s, 4H), 2.49 (s, 3H), 1.13 (s, 6H); ^{13}C NMR (125 MHz, Acetone-d_6): δ 151.7, 142.8, 136.1, 130.0, 120.7, 73.0, 32.3, 22.5, 21.5; ^{11}B (64 MHz, Acetone-d_6): δ 28.1; IR (CH_2Cl_2 cast): 2941, 1519, 1352, 1282 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{12}H_{16}O_4N^{11}B$ 249.11723, found 249.11772.

5.4.2.6 2-Nitro-6-methylphenylboronic acid, (+)-pinanediol ester 30

A solution of boronate **29** (48 mg, 0.19 mmol) and (+)-pinanediol **25** (44 mg, 0.26 mmol) in THF (2.5 mL) and water (1 mL) was stirred at RT under argon for 48 h. The mixture was then concentrated, diluted with water (5 mL) and extracted with ether

(3 x 5 mL). The combined ether layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to give the crude product as an oil (106 mg). Flash chromatography (25% EtOAc/Hexanes, 5.6 g SiO_2) gave the product as brown crystals (23 mg, 0.072 mmol, 38%) that were contaminated with ~2% of the initial boronate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 1H), 7.45 (m, 1H), 7.37 (m, 1H), 4.56 (dd, *J* = 8.9 Hz, 2.6 Hz, 1H), 2.50 (s, 3H), 2.45 (m, 1H), 2.28 (m, 1H), 2.14 (m, 1H), 1.98 (m, 2H), 1.70 (d, *J* = 11.4, 1H), 1.55 (s, 3H), 1.32 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.3, 143.0, 135.2, 129.6, 120.4, 86.8, 78.4, 51.4, 39.7, 38.6, 35.4, 28.3, 27.1, 26.4, 24.3, 22.0; ^{11}B (64 MHz, Acetone-d_6): δ 29.7; IR (CH_2Cl_2 cast): 2928, 1617, 1349 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{17}H_{22}O_4N^{11}B$ 315.16418, found 315.16508.

5.4.3 Preparation of N-Acryloylaminoarylboronic esters

5.4.3.1 *N-Acryloylaniline 22*

This compound was prepared according to the literature procedure.[17]

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (m, 2H), 7.31 (m, 2H), 7.18 (br s, 1H), 7.10 (m, 1H), 6.43 (d, *J* = 17 Hz, 1H), 6.25 (dd, *J* = 17 Hz, 10.2 Hz, 1H), 5.78 (d, *J* = 10 Hz, 1H); ^{13}C ($CDCl_3$, 75 MHz): δ 164.0, 140.2, 132.8, 129.5, 126.9, 124.4, 120.3.

5.4.3.2 *2-N-Acryloylaminophenylboronic acid, pinacol ester 13a*

A solution of aniline **15a** (296 mg, 1.35 mmol), pyridine (0.22 mL, 2.7 mmol) and DMAP (42 mg, 0.34 mmol) in THF (5 mL) at 0 °C was treated dropwise with a solution of acryloyl chloride (152 mg, 1.68 mmol) in THF (2.5 mL). After 1 h the mixture was warmed to RT and left to stir for 4 h. The thick white slurry was then partitioned between brine (20 mL) and THF (20 mL). The layers were separated and the aqueous layer was extracted with THF (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a light brown solid which was dried under vacuum overnight to give the product (181.3 mg, 49%).

^{1}H NMR (Acetone-d_6, 400 MHz): δ 10.34 (br s, 1H), 8.06 (m, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.37 (m, 1H), 7.10 (apparent t, *J* = 8 Hz, 1H), 6.38 (m, 2H), 5.82 (dd, *J* = 7 Hz, 5 Hz, 1H), 1.38 (s, 12H); ^{13}C NMR (Acetone-d_6, 100 MHz): δ 164.1, 143.6, 136.0, 135.9, 132.2, 131.8, 131.7, 127.9, 127.8, 124.6, 124.5, 119.0, 84.1, 84.0, 25.6, 25.5; ^{13}C NMR (Benzene-d_6, 100 MHz): δ 163.2, 145.3, 136.4, 133.1, 132.8, 125.8, 123.4, 119.6, 83.9, 24.8. A very slight peak duplication effect, ca. 0.05 ppm, was observed for arene carbons in acetone. This duplication may be due to a slow competing effect from this coordinating solvent; ^{11}B NMR (Benzene-d_6, 64 MHz): δ 30.1; IR (CH_2Cl_2 cast) 3316, 3058, 2970, 1646, 731 cm^{-1}; HR-MS (EI): Calculated for $C_{15}H_{20}NO_3{}^{11}B$, 273.15363, Found, 273.15376.

5.4.3.3 4-N-Acryloylaminophenylboronic acid, pinacol ester 20

A slurry of 4-aminophenylboronic acid hydrochloride pinacol ester **19** (524 mg, 2.05 mmol), triethylamine (0.85 mL, 6.1 mmol) and DMAP (45 mg, 0.37 mmol) in THF (7.5 mL) at 0 °C was treated dropwise with a solution of acryloyl chloride (1.9 mL, 2.3 mmol) in THF (2.5 mL). The resulting mixture was stirred at 0 °C for 2 h and then at RT overnight. The thick mixture was then diluted with brine (25 mL) and water was added to make the mixture homogenous. The layers were separated and the aqueous phase was extracted with THF (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and evaporate. Flash chromatography (20% EtOAc/Toluene, 51 g SiO_2) gave the pure product as a white solid (0.38 g, 1.4 mmol, 68%).

^{1}H NMR (Acetone-d_6, 300 MHz): δ 7.75 (AB, J = 9 Hz, 2H), 7.68 (AB, J = 9 Hz, 2H), 6.46 (dd, J = 17 Hz, 10 Hz, 1H), 6.34 (dd, J = 16 Hz, 3 Hz, 1H), 5.70 (dd, J = 10 Hz, 3 Hz, 1H), 1.31 (s, 12H); ^{13}C NMR (Acetone-d_6, 100 MHz): δ 164.1, 142.8, 136.3, 136.2 (broad), 132.7, 127.4, 119.2, 84.3, 25.2; ^{11}B NMR (Benzene-d_6, 64 MHz): δ 30.8; IR (CH_2Cl_2 cast) 3303, 3102, 2978, 1667, 1635, 1593, 1361, 860 cm^{-1}; HR-MS (EI): Calculated for $C_{15}H_{20}NO_3{}^{11}B$, 273.15363, Found, 273.15381.

5.4.3.4 2-N-Acryloylaminophenylboronic acid, (+)-pinanediol ester 13b

As per **13a**, with the aniline **15b** (613 mg, 2.26 mmol), pyridine (0.37 mL, 4.5 mmol), and DMAP (29 mg, 0.24 mmol) in THF (25 mL), and acryloyl chloride (243 mg, 2.69 mmol) in THF (5 mL). Once the reaction was complete, the mixture was diluted with brine (25 mL) and the layers were separated. The aqueous layer was then extracted with THF (3 x 25 mL). The combined THF layers were then washed with 0.1 M H_2SO_4/brine (10 mL), saturated $NaHCO_3$ (2 x 20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated to give the crude product as a white solid (619 mg, 1.90 mmol, 84%).

^{1}H NMR (300 MHz, C_6D_6): 9.73 (br s, 1H), 9.16 (d, J= 8.4 Hz, 1H), 8.06 (dd, J= 7.4 Hz, 1.2 Hz, 1H), 7.29 (dd, J= 8.8 Hz, 1.5 Hz, 1H), 6.93 (t, J= 7.4 Hz, 1H), 6.40 (dd, J= 17.0 Hz, 1.0 Hz, 1H), 6.17 (dd, *J*= 17.0 Hz, 10.3 Hz, 1H), 5.29 (dd, *J*= 10.4 Hz, 1.1 Hz, 1H), 4.09 (dd, *J*= 8.5 Hz, 1.6 Hz, 1H), 2.04 (m, 1H), 2.00 (m, 1H), 1.94 (m, 1H), 1.79 (m, 1H), 1.57 (m, 1H), 1.19 (s, 3H), 1.14 (m, 1H), 1.03 (s, 3H), 0.49 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 163.2, 145.4, 136.6, 133.4, 132.9, 125.9, 123.4, 119.8, 86.6, 78.2, 51.6, 39.7, 38.0, 35.5, 28.6, 26.9, 26.6, 23.8; ^{11}B NMR (64 MHz, C_6D_6): δ 30.4; IR (CH_2Cl_2 cast): 3362, 3054, 2924, 1644, 1628, 1050, 735 cm^{-1}; HRMS (EI, *m/z*) Calcd for $C_{19}H_{24}NO_3{}^{11}B$, 325.18494, found 325.18508.

5.4.3.5 2-N-Acryloylaminophenylboronic acid, (-)-1,2-dicyclohexyl-1,2-ethanediol ester 13c

As per **13a**, with the aniline **15c** (211 mg, 0.646 mmol), pyridine (0.10 mL, 1.2 mmol), and DMAP (catalytic amount) in THF (6 mL), and acryloyl chloride (73 mg, 0.80 mmol) in THF (1 mL). Work-up gave the product as an off white solid (188 mg, 0.510 mmol, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (br s, 1H), 8.56 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.45 (ap t, *J* = 7.7 Hz, 1H), 7.10 (ap t, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 16.5 Hz, 1H), 6.20 (dd, *J* = 16.8 Hz, 9.9 Hz, 1H), 5.72 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 4.2 Hz, 2H), 2.0-1.0 (m, 22H + Hydrocarbon impurities); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 163.6, 135.7, 131.6, 131.0, 128.0, 124.5, 118.9, 84.4, 75.4, 43.5, 40.8, 30.1, 29.6, 28.6, 28.2, 26.9, 26.7, 26.5, 26.4; ^{11}B NMR (64 MHz, C_6D_6): δ 29.6; IR (Microscope) 3278, 1647, 1575 cm^{-1}; HRMS (EI, *m/z*) Calcd for $C_{23}H_{32}O_3{}^{11}BN$ 381.24753, found 381.24790.

5.4.3.6 2-N-Acryloylaminophenylboronic acid, (2R, 3R)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol ester 13d

A solution of the aniline **15d** (346 mg, 0.624 mmol), pyridine (100 µL, 1.24 mmol), and DMAP (15 mg, 0.12 mmol) in THF (3 mL) at 0 °C was treated slowly with acryloyl chloride (55 µL, 0.68 mmol). The resulting mixture was stirred at 0°C for 1 h then at RT for 4 h before being worked-up as per **13a**. Flash chromatography (5% EtOAc/Toluene, 20 g SiO_2) gave the product as a colourless glass (209 mg, 0.343 mmol, 55%).

^{1}H NMR (500 MHz, C_6D_6): δ 9.06 (d, *J* = 8.3 Hz, 1H), 8.70 (br s, 1H), 7.48 (m, 9H), 7.2-6.9 (m, 13H), 6.68 (dt, *J* = 7.4 Hz, 1.0 Hz, 1H), 6.31 (dd, *J* = 16.8 Hz, 1.6 Hz, 1H), 5.78 (s, 2H), 5.46 (dd, *J* = 16.8 Hz, 10.2 Hz, 1H), 5.17 (dd, *J* = 10.3 Hz, 1.7 Hz, 1H), 2.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 143.6, 140.6, 140.2, 135.8, 132.5, 131.8, 129.6, 128.3, 128.0, 127.8, 127.6, 127.5, 126.5, 122.8, 119.1, 83.4, 78.5, 51.9; ^{11}B NMR

(64 MHz, $CDCl_3$): δ 30.5; IR (CH_2Cl_2 cast): 3377, 3057, 2938, 1693, 1611, 1348, 760, 701 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{39}H_{36}O_5N^{11}B$ 609.26868, found 609.26921.

5.4.3.7 2-N-Acryloylamino-6-methylphenylboronic acid, (+)-pinanediol ester 13e

Nitro compound **30** (36 mg, 0.11 mmol) was hydrogenated in a Parr bottle over 10% Pd/C (4 mg) in EtOH (2 mL) at RT under 45 psi H_2 for 4 h. The mixture was filtered through Celite® and the pad was washed with EtOH (5 x 1 mL). The combined alcohol filtrates were concentrated to give the crude aniline (31 mg, 94%) as a yellow oil. This oil was dissolved in THF (0.8 mL), cooled to 0 °C and treated successively with DMAP (8 mg, 0.07 mmol), pyridine (25 μL, 0.30 mmol) and acryloyl chloride (16 μL, 0.20 mmol). The thick mixture was then stirred at RT for 90 min. It was then diluted with brine (2 mL) and extracted with THF (4 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4) and concentrated to give the crude product (35 mg). Flash chromatography (5% EtOAc/toluene, 16 g SiO_2) and Kugelrohr distillation (250 °C, 0.1 torr) gave the pure product (15 mg, 0.045 mmol, 40%).

^1H NMR (500 MHz, Acetone-d_6): δ 9.88 (br s, 1H), 7.81 (m, 1H), 7.24 (ap t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.34 (m, 2H), 5.78 (dd, *J* = 8.4 Hz, 3.4 Hz, 1H), 4.53 (dd, *J* = 8.7 Hz, 1.9 Hz, 1H), 2.52 (s, 3H), 2.46 (m, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 2.1-1.9 (m, 2H), 1.52 (s, 3H), 1.44 (m, 1H), 1.31 (s, 3H), 1.30 (m, 1H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 146.2, 144.6, 132.6, 131.6, 126.2, 126.0, 117.6, 86.3, 77.6, 51.4, 39.6, 38.2, 35.5, 28.7, 27.0, 26.5, 24.0, 23.4; ^{11}B (64 MHz, Acetone-d_6) δ 30.0; IR (CH_2Cl_2 cast): 2915, 1640, 1627 cm^{-1}; HRMS (EI, *m/z*): Calcd for $C_{20}H_{26}O_3N^{11}B$ 339.20056, found 339.20054.

5.5 References

(1) Ishihara, K. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; WILEY-VCH: Weinheim, **1999**; Vol. 1, pp 135-190.

(2) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons, Inc.: New York, **1995**.

(3) Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7517-7518.

(4) Molander, G. A.; Bobbitt, K. L.; Murray, C. K. *J. Am. Chem. Soc.* **1992**, *114*, 2759-2760.

(5) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1994**, *59*, 2676-2678.

(6) Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3362-3374.

(7) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510-3512.

(8) Larsen, D. S.; OShea, M. D.; Brooker, S. *Chem. Commun.* **1996**, 203-204.

(9) Larsen, D. S.; Oshea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1019-1028.

(10) Krohn, K.; Micheel, J.; Zukowski, M. *Tetrahedron* **2000**, *56*, 4753-4758.

(11) Hughes, M. P.; Shang, M. Y.; Smith, B. D. *J. Org. Chem.* **1996**, *61*, 4510-4511.

(12) Hughes, M. P.; Smith, B. D. *J. Org. Chem.* **1997**, *62*, 4492-4499.

(13) Kennedy, J. W. J.; Hall, D. G. *J. Organomet. Chem.* **2003**, in press.

(14) Kennedy, J. W. J.; Hall, D. G. *Synlett* **2002**, 477-479.

(15) Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711-723.

(16) Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597-7605.

(17) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583-3587.

(18) Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917-2951.

(19) Matteson, D. S.; Man, H. W. *J. Org. Chem.* **1993**, *58*, 6545-6547.

(20) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287-8297.

(21) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510.

(22) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447-3450.

(23) Matteson, D. S.; Michnick, T. J.; Willett, R. D.; Patterson, C. D. *Organometallics* **1989**, *8*, 726-729.

Chapter 6

Thesis Conclusions

This thesis describes research aimed at the efficient generation of stereogenic quaternary carbon centres. Over the course of these studies, we were able to demonstrate that these sterically congested centres are readily available via the stereospecific reaction of γ-disubstituted β-carboxyester allylboronates with aldehydes. This reaction generates exo-methylene butyrolactone products which contain the desired quaternary carbon centre.

The success of this allylboration reaction hinges on the availability of stereochemically pure γ-disubstituted allylboronates. The one pot, two step carbocupration-alkylation sequence developed in the initial phase of this project allows for the rapid and efficient preparation of these boronates. This preparation is only successful if an additive is used along with the electrophile in the alkylation step. In the presence of HMPA, a wide variety of γ-disubstituted allylboronates can be made from simple alkynoate esters in good yield and with excellent control of the olefin geometry.

The subsequent reaction of these allylboronates with aldehydes are operationally simple. Combination of the two reagents, with or without solvent, leads to the clean formation of an exo-methylene butyrolactone bearing a quaternary carbon centre. Furthermore, these reactions are stereospecific, and the lactone substituent that originated from the aldehyde is always *syn* to the substituent which originated from the cuprate. This stereochemical outcome does not depend on the nature of these groups, but only on how they were introduced into the sequence. Consequently, either diastereomer of the desired quaternary carbon centre can be generated by carefully choosing which group to introduce through the cuprate, the alkynoate and the aldehyde. This remarkable versatility is one of the biggest advantages of this methodology.

The unusual presence of the β-carboxyester in our allylboronates gave us the opportunity to explore the ability of a chiral carboxyester to control the absolute stereochemistry of an allylboration. We were able to show that this novel method for stereocontrol is reasonably effective, and could provide enantioselectivities of over 80%. Unfortunately, we were not able to find a single auxiliary that could provide truly effective levels of stereoinduction. However, these allylborations can be performed with exceptional levels of enantioselectivity using an allylboronate bearing two chiral directing groups.

Selectivities of over 98% can be obtained using a matched combination of auxiliaries on both the boronic ester and the carboxyester groups. Conveniently, both auxiliaries are cleaved from the product butyrolactone in the final cyclization step. This self-removal feature, along with the high enantioselectivities, help compensate for the requirement of two separate auxiliaries.

In addition to being biologically interesting targets in their own right, the highly functionalized exo-methylene butyrolactones produced in these allylborations are versatile synthetic intermediates. We demonstrated that the olefin can be stereoselectively reduced to generate a butyrolactone with three contiguous stereocentres, one of which is a quaternary carbon centre. Although we have yet to show extensive further transformation of this product, we believe that it could someday be an important intermediate in a total synthesis.

Despite all these advantages, the allylboration reaction came with one serious limitation – the reaction was extremely slow. Reactions took about 2 weeks at room temperature to reach completion. Although heating allowed for more reasonable reaction times, the stereospecificity of the reaction was sometimes lost at elevated temperatures. This sluggishness inspired us to seek a way to make our reaction more efficient, and turned us on to the possibility of catalyzing the reaction.

The most important discovery to come from this thesis is the development of the Lewis acid catalysed allylboration reaction. This reaction was virtually unknown prior to our studies. We showed that catalytic amounts of several different metal triflates were able to provide a dramatic rate enhancement in the reaction of our β-carboxyester allylboronates compared to the uncatalysed process. Of all these possibilities, scandium triflate and copper triflate stood out as being especially effective. The observed catalytic effect is quite remarkable. Under this new catalytic manifold, reactions that previously took two weeks at room temperature are now complete after stirring overnight at room temperature. This catalysis not only provides a large rate enhancement over the non-catalysed process but also broadens the scope of aldehydes that may be used as substrates. Hindered aliphatic aldehydes which give poor yields in the non-catalysed allylboration are viable substrates under Lewis acid catalysis.

A very important feature of this catalytic effect is that it does not disrupt the high levels of stereoselectivity that one has come to expect from reactions with allylboronates. This finding is truly a significant breakthrough in allylboration chemistry, and it constitutes the first example of a metal-catalysed allylation with allylboronates. As testimony to the importance of this finding, a second group independently published their findings on this subject within weeks of our initial report.

The ultimate aim of this project would be to develop a chiral version of the catalysed reaction. Unfortunately, preliminary studies with some of the common chiral systems for scandium catalysts did not yield promising results and this goal remains elusive.

While a systematic survey of other catalysts and ligands might eventually lead to a successful enantioselective allylboration system, a deeper understanding of the reaction mechanism would allow for a more effective and rational approach to solving this problem. Although the origin of this catalytic effect is still under investigation, our preliminary results suggest that it derives from an electrophilic activation of the boron atom. We believe that the catalyst binds to one or both of the boronate oxygens and disrupts lone pair conjugation between the oxygen and the empty p-orbital of the boron, thereby increasing the electrophilicity of the boron. While much more work needs to be done to establish this hypothesis as fact, it does raise the exciting possibility that this boronate activation concept might find applications outside the realm of allylboration chemistry.

One of these applications might be the use of boronic esters as Lewis acid catalysts. In a side project to the one focusing on the generation of quaternary carbon centres, we also investigated the possibility that a weak boronic ester could act as an intramolecular catalyst. We found that an acrylamide derived from 2-aminophenylboronic ester underwent a notably faster Diels-Alder reaction and showed higher *endo*:*exo* selectivity than the corresponding system where boron was absent. This increased activity was attributed to the internal coordination of the acrylamide carbonyl to the boronic ester. Although we were able to validate this concept of internal activation, the levels of rate acceleration observed in the current system were too low for practical uses. An intriguing thought is to see if the boronate in this system could be activated by an external Lewis acid. If an appropriate catalyst could be found, then increasing the electrophilicity of the boron would strengthen the internal coordination to the carbonyl, and thus might turn this system from an academic curiosity into an effective synthetic methodology.

Appendices

X-Ray Crystallography Reports

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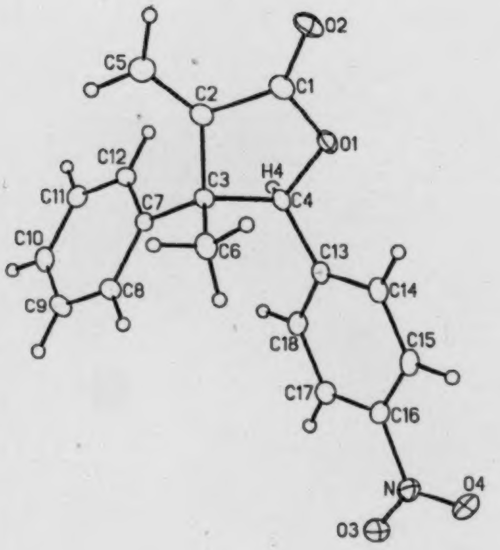
Appendix A

Structure report for Lactone 21n (Chapter 3)

University of Alberta Department of Chemistry

X-Ray Crystallography Laboratory

XCL Code: DGH0203
Date: 4 April 2002
Compound: 4-methyl-3-methylene-5-*p*-nitrophenyl-4-phenyldihydrofuran-2(3H)-one
Formula: $C_{18}H_{15}NO_4$
Supervisor: D. G. Hall **Crystallographer:** M. J. Ferguson



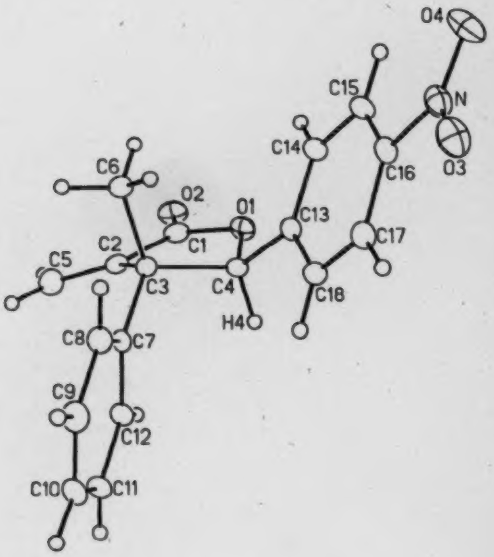


Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{18}H_{15}NO_4$
formula weight	309.31
crystal dimensions (mm)	0.34 × 0.28 × 0.15
crystal system	monoclinic
space group	*C*2/*c* (No. 15)
unit cell parameters[a]	
a (Å)	13.6632 (13)
b (Å)	9.8807 (9)
c (Å)	22.901 (2)
β (deg)	98.491 (2)
V (Å^3)	3057.8 (5)
Z	8
ρ_{calcd} (g cm^{-3})	1.344
μ (mm^{-1})	0.096
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.2°) (25 s exposures)
data collection 2θ limit (deg)	52.80
total data collected	8325 ($-17 \le h \le 17$, $-12 \le k \le 9$, $-28 \le l \le 28$)
independent reflections	3143 ($R_{\text{int}} = 0.0379$)
number of observed reflections (*NO*)	2330 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9858–0.9682
data/restraints/parameters	3143 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 208
goodness-of-fit (S)[e]	1.024 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[f]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0439
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1109
largest difference peak and hole	0.250 and –0.164 e Å^{-3}

(continued)

Table 1. Crystallographic Experimental Details (continued)

[a] Obtained from least-squares refinement of 2947 reflections with $5.11° < 2\theta < 51.98°$.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c] Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d] Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted R-factors wR_2 and all goodnesses of fit S are based on F_o^2; conventional R-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. R-factors based on F_o^2 are statistically about twice as large as those based on F_o, and R-factors based on ALL data will be even larger.

[e] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0496P)^2 + 1.2237P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	x	y	z	U_{eq}, Å^2
O1	0.10517(9)	0.79345(11)	0.42449(5)	0.0385(3)*
O2	0.26342(10)	0.85952(13)	0.44336(6)	0.0512(4)*
O3	-0.36983(10)	0.61485(16)	0.25537(6)	0.0606(4)*
O4	-0.33200(12)	0.81750(16)	0.23114(7)	0.0696(5)*
N	-0.31483(12)	0.71358(18)	0.26017(7)	0.0484(4)*
C1	0.20447(13)	0.77057(18)	0.42888(7)	0.0376(4)*
C2	0.22182(12)	0.62843(17)	0.41313(7)	0.0335(4)*
C3	0.12284(11)	0.56867(16)	0.38650(6)	0.0291(3)*
C4	0.05200(12)	0.66601(15)	0.41490(7)	0.0300(4)*
C5	0.31061(13)	0.5740(2)	0.42043(9)	0.0475(5)*
C6	0.11281(13)	0.59161(18)	0.31943(7)	0.0394(4)*
C7	0.10646(10)	0.42219(15)	0.40317(7)	0.0278(3)*
C8	0.05794(12)	0.32983(17)	0.36310(8)	0.0368(4)*
C9	0.04349(13)	0.19733(18)	0.37971(9)	0.0444(5)*
C10	0.07650(13)	0.15426(18)	0.43638(9)	0.0427(4)*
C11	0.12263(12)	0.24561(18)	0.47708(8)	0.0387(4)*
C12	0.13752(11)	0.37846(16)	0.46094(7)	0.0334(4)*
C13	-0.04695(12)	0.68814(16)	0.37777(7)	0.0315(4)*
C14	-0.06571(13)	0.79881(17)	0.34010(8)	0.0375(4)*
C15	-0.15439(14)	0.80909(18)	0.30249(8)	0.0406(4)*
C16	-0.22309(12)	0.70722(18)	0.30284(7)	0.0376(4)*
C17	-0.20818(12)	0.59793(18)	0.34067(8)	0.0386(4)*
C18	-0.11965(12)	0.58951(17)	0.37842(7)	0.0360(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.364(2)	C7	C8	1.391(2)
O1	C4	1.4541(18)	C7	C12	1.397(2)
O2	C1	1.205(2)	C8	C9	1.386(2)
O3	N	1.226(2)	C9	C10	1.377(3)
O4	N	1.227(2)	C10	C11	1.381(3)
N	C16	1.473(2)	C11	C12	1.387(2)
C1	C2	1.478(2)	C13	C14	1.393(2)
C2	C3	1.519(2)	C13	C18	1.393(2)
C2	C5	1.315(2)	C14	C15	1.383(2)
C3	C4	1.572(2)	C15	C16	1.377(3)
C3	C6	1.538(2)	C16	C17	1.381(2)
C3	C7	1.522(2)	C17	C18	1.381(2)
C4	C13	1.503(2)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C4	109.68(12)	C3	C7	C8	122.13(14)
O3	N	O4	123.48(17)	C3	C7	C12	119.77(13)
O3	N	C16	118.41(16)	C8	C7	C12	118.06(15)
O4	N	C16	118.11(17)	C7	C8	C9	120.81(17)
O1	C1	O2	121.09(17)	C8	C9	C10	120.71(17)
O1	C1	C2	109.46(13)	C9	C10	C11	119.18(16)
O2	C1	C2	129.46(17)	C10	C11	C12	120.59(17)
C1	C2	C3	107.59(14)	C7	C12	C11	120.61(15)
C1	C2	C5	122.41(16)	C4	C13	C14	122.17(15)
C3	C2	C5	129.96(16)	C4	C13	C18	118.38(14)
C2	C3	C4	99.33(12)	C14	C13	C18	119.31(15)
C2	C3	C6	106.64(13)	C13	C14	C15	120.51(16)
C2	C3	C7	115.11(13)	C14	C15	C16	118.55(16)
C4	C3	C6	110.69(13)	N	C16	C15	118.63(16)
C4	C3	C7	110.84(12)	N	C16	C17	118.82(16)
C6	C3	C7	113.32(13)	C15	C16	C17	122.53(16)
O1	C4	C3	105.54(12)	C16	C17	C18	118.31(16)
O1	C4	C13	110.31(12)	C13	C18	C17	120.73(16)
C3	C4	C13	114.35(12)				

Appendix B

Structure Report for Boronate 27f (Chapter 3)

University of Alberta Department of Chemistry

X-Ray Crystallography Laboratory

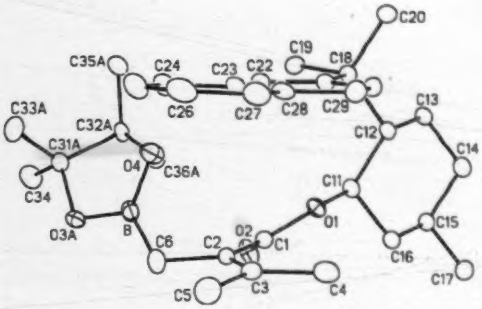
XCL Code: DGH0101

Date: 4 October 2001

Compound: (1*R*, 2*S*, 5*R*)-5-Methyl-2-(1-methyl-1-(2-naphthyl)ethyl)cyclohexyl 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl)methylbut-2-enoate

Formula: $C_{32}H_{45}BO_4$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



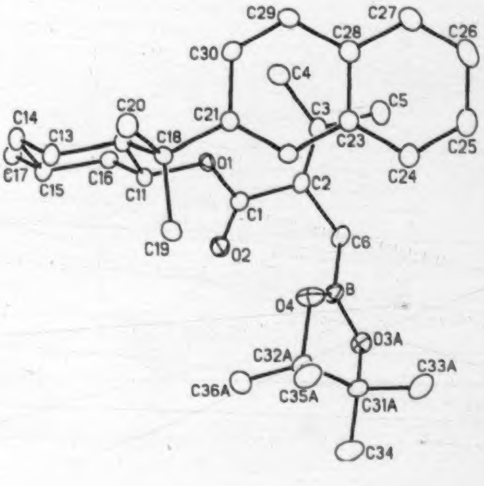


Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{32}H_{45}BO_4$
formula weight	504.49
crystal dimensions (mm)	0.66 x 0.30 x 0.06
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	10.9195 (14)
b (Å)	14.2580 (18)
c (Å)	19.034 (2)
V (Å^3)	2963.4 (7)
Z	4
ρ_{calcd} (g cm^{-3})	1.131
μ (mm^{-1})	0.072
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.2°) (25 s exposures)
data collection 2θ limit (deg)	52.88
total data collected	16416 ($-13 \le h \le 13$, $-15 \le k \le 17$, $-23 \le l \le 23$)
independent reflections	6087 ($R_{\text{int}} = 0.0819$)
number of observed reflections (*NO*)	3838 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9957–0.9541
data/restraints/parameters	6087 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 331
Flack absolute structure parameter[e]	0.3 (15)
goodness-of-fit (S)[f]	1.010 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0606
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1284
largest difference peak and hole	0.156 and –0.170 e Å^{-3}

[a] Obtained from least-squares refinement of 5822 centered reflections.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c] Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d] Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

[e] Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. In this case, although the Flack parameter has refined to a value indicative of a degree of racemic twinning, the large value of the standard error for this parameter and the presence of only light atoms (oxygen, carbon, boron and hydrogen) in the molecule suggest that absolute configuration cannot be assigned based on X-ray data alone. In this case the assignment of absolute configuration is based upon the known stereochemistry of the precursor compound.

[f] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0469P)^2 + 0.1044P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	x	y	z	U_{eq}, Å^2
O1	0.34980(15)	-0.00394(13)	-0.06217(9)	0.0356(5)*
O2	0.48299(19)	-0.00619(17)	-0.15164(10)	0.0550(6)*
O3A[a]	0.3699(4)	0.0917(2)	-0.33427(17)	0.0455(9)*
O3B[b]	0.4313(7)	0.0876(6)	-0.3209(4)	0.053(2)
O4	0.3229(2)	0.14597(16)	-0.22741(11)	0.0608(7)*
C1	0.3818(3)	-0.0218(2)	-0.12917(14)	0.0361(7)*
C2	0.2796(3)	-0.0594(2)	-0.17319(14)	0.0380(7)*
C3	0.1920(3)	-0.1147(2)	-0.14864(15)	0.0392(7)*
C4	0.1803(3)	-0.1491(2)	-0.07386(15)	0.0520(8)*
C5	0.0900(3)	-0.1516(3)	-0.19530(18)	0.0639(10)*
C6	0.2950(3)	-0.0324(2)	-0.25027(15)	0.0543(9)*
C11	0.4411(2)	0.0373(2)	-0.01560(13)	0.0334(7)*
C12	0.3713(2)	0.0910(2)	0.04220(13)	0.0336(7)*
C13	0.4683(3)	0.1293(2)	0.09379(14)	0.0397(7)*
C14	0.5510(3)	0.0527(2)	0.12351(14)	0.0436(8)*
C15	0.6162(2)	-0.0020(2)	0.06564(14)	0.0397(7)*
C16	0.5215(3)	-0.0403(2)	0.01429(14)	0.0381(7)*
C17	0.6963(3)	-0.0795(2)	0.09538(15)	0.0467(8)*
C18	0.2812(2)	0.1679(2)	0.01442(14)	0.0336(7)*
C19	0.3461(3)	0.2320(2)	-0.03892(14)	0.0397(7)*
C20	0.2381(3)	0.2310(2)	0.07581(14)	0.0432(8)*
C21	0.1658(2)	0.12318(19)	-0.01662(13)	0.0319(6)*
C22	0.1278(2)	0.1370(2)	-0.08447(13)	0.0341(7)*
C23	0.0168(2)	0.0996(2)	-0.11097(14)	0.0360(7)*
C24	-0.0219(3)	0.1166(2)	-0.18102(14)	0.0454(8)*
C25	-0.1314(3)	0.0830(3)	-0.20403(17)	0.0564(10)*
C26	-0.2070(3)	0.0295(2)	-0.15969(17)	0.0547(9)*
C27	-0.1710(3)	0.0101(2)	-0.09250(16)	0.0473(8)*
C28	-0.0583(2)	0.0452(2)	-0.06637(15)	0.0370(7)*
C29	-0.0181(3)	0.0299(2)	0.00376(15)	0.0396(7)*
C30	0.0889(2)	0.0675(2)	0.02682(14)	0.0358(7)*
C31A[a]	0.3797(5)	0.1939(3)	-0.3385(2)	0.0402(11)*
C32A[a]	0.3975(6)	0.2219(3)	-0.2600(2)	0.0404(13)*
C33A[a]	0.2607(6)	0.2252(5)	-0.3709(3)	0.0676(18)*
C31B[b]	0.4574(10)	0.1897(8)	-0.3146(5)	0.054(3)
C32B[b]	0.3451(12)	0.2281(10)	-0.2817(8)	0.066(4)
C33B[b]	0.5712(11)	0.1973(10)	-0.2692(6)	0.069(4)
C34	0.4861(4)	0.2221(3)	-0.38692(18)	0.0717(11)*
C35A[a]	0.3358(8)	0.3127(5)	-0.2418(4)	0.061(2)*
C36A[a]	0.5292(6)	0.2130(4)	-0.2344(3)	0.0650(17)*

Table 2. Atomic Coordinates and Displacement Parameters (continued)

Atom	x	y	z	U_{eq}, Å^2
C35B[b]	0.3780(13)	0.3151(13)	-0.2262(8)	0.052(5)
C36B[b]	0.2423(14)	0.2460(11)	-0.3328(7)	0.091(5)
B	0.3367(4)	0.0687(3)	-0.26835(18)	0.0458(9)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$. [a]Refined with an occupancy factor of 0.65. [b]Refined with an occupancy factor of 0.35.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance
O1	C1	1.346(3)
O1	C11	1.458(3)
O2	C1	1.205(3)
O3A	C31A	1.463(6)
O3A	B	1.347(5)
O3B	C31B	1.487(13)
O3B	B	1.464(8)
O4	C32A	1.489(5)
O4	C32B	1.581(14)
O4	B	1.358(4)
C1	C2	1.496(4)
C2	C3	1.324(4)
C2	C6	1.526(4)
C3	C4	1.511(4)
C3	C5	1.519(4)
C6	B	1.550(5)
C11	C12	1.542(4)
C11	C16	1.523(4)
C12	C13	1.544(4)
C12	C18	1.565(4)
C13	C14	1.526(4)
C14	C15	1.526(4)
C15	C16	1.524(4)
C15	C17	1.519(4)
C18	C19	1.540(4)
C18	C20	1.548(4)
C18	C21	1.530(4)
C21	C22	1.371(3)
C21	C30	1.421(4)
C22	C23	1.417(4)
C23	C24	1.420(4)
C23	C28	1.413(4)
C24	C25	1.360(4)
C25	C26	1.406(5)
C26	C27	1.366(4)
C27	C28	1.418(4)
C28	C29	1.422(4)
C29	C30	1.358(4)
C31A	C32A	1.559(7)
C31A	C33A	1.505(8)
C31A	C34	1.536(6)
C32A	C35A	1.500(9)
C32A	C36A	1.524(9)
C31B	C32B	1.481(17)
C31B	C33B	1.517(15)
C31B	C34	1.485(10)
C32B	C35B	1.67(2)
C32B	C36B	1.507(18)

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C11	118.3(2)	C24	C23	C28	119.0(3)
C31A	O3A	B	108.3(3)	C23	C24	C25	120.3(3)
C31B	O3B	B	105.1(6)	C24	C25	C26	120.9(3)
C32A	O4	B	106.9(3)	C25	C26	C27	120.2(3)
C32B	O4	B	102.1(6)	C26	C27	C28	120.4(3)
O1	C1	O2	122.6(3)	C23	C28	C27	119.1(3)
O1	C1	C2	113.9(2)	C23	C28	C29	117.9(2)
O2	C1	C2	123.5(2)	C27	C28	C29	122.9(3)
C1	C2	C3	123.7(3)	C28	C29	C30	120.6(3)
C1	C2	C6	111.4(3)	C21	C30	C29	122.7(3)
C3	C2	C6	124.7(3)	O3A	C31A	C32A	102.1(4)
C2	C3	C4	125.9(3)	O3A	C31A	C33A	104.7(4)
C2	C3	C5	122.0(3)	O3A	C31A	C34	110.4(4)
C4	C3	C5	112.1(3)	C32A	C31A	C33A	115.1(5)
C2	C6	B	118.7(3)	C32A	C31A	C34	114.5(4)
O1	C11	C12	107.24(19)	C33A	C31A	C34	109.3(4)
O1	C11	C16	109.2(2)	O4	C32A	C31A	98.4(4)
C12	C11	C16	112.3(2)	O4	C32A	C35A	106.6(4)
C11	C12	C13	106.9(2)	O4	C32A	C36A	108.8(4)
C11	C12	C18	114.7(2)	C31A	C32A	C35A	112.7(5)
C13	C12	C18	113.5(2)	C31A	C32A	C36A	113.7(5)
C12	C13	C14	112.9(2)	C35A	C32A	C36A	114.9(5)
C13	C14	C15	112.0(2)	O3B	C31B	C32B	103.8(9)
C14	C15	C16	109.3(2)	O3B	C31B	C33B	105.8(9)
C14	C15	C17	111.8(2)	O3B	C31B	C34	105.7(7)
C16	C15	C17	111.6(3)	C32B	C31B	C33B	114.2(10)
C11	C16	C15	111.7(2)	C32B	C31B	C34	116.8(10)
C12	C18	C19	110.4(2)	C33B	C31B	C34	109.4(8)
C12	C18	C20	110.1(2)	O4	C32B	C31B	97.4(9)
C12	C18	C21	110.9(2)	O4	C32B	C35B	99.8(10)
C19	C18	C20	107.0(2)	O4	C32B	C36B	115.6(11)
C19	C18	C21	111.8(2)	C31B	C32B	C35B	111.4(11)
C20	C18	C21	106.5(2)	C31B	C32B	C36B	114.0(12)
C18	C21	C22	123.6(2)	C35B	C32B	C36B	116.3(12)
C18	C21	C30	119.6(2)	O3A	B	O4	111.5(3)
C22	C21	C30	116.7(2)	O3A	B	C6	120.9(3)
C21	C22	C23	122.7(3)	O3B	B	O4	108.7(4)
C22	C23	C28	121.7(3)	O3B	B	C6	122.1(4)
C22	C23	C28	119.3(2)	O4	B	C6	126.5(3)

Appendix C

Structure Report for Enantiopure Lactone 36c

(Chapter 3)

University of Alberta Department of Chemistry

X-Ray Crystallography Laboratory

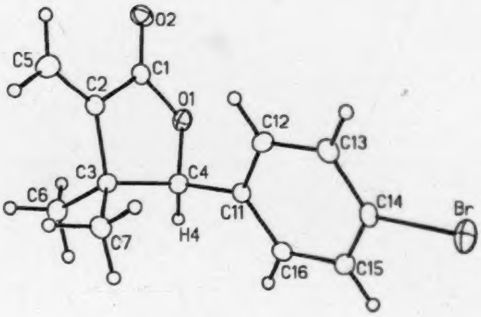
XCL Code: DGH0301

Date: 24 June 2003

Compound: (5*S*)-5-(4-Bromophenyl)-4,4-dimethyl-3-methylenedihydrofuran-2(3*H*)-one

Formula: $C_{13}H_{13}BrO_2$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



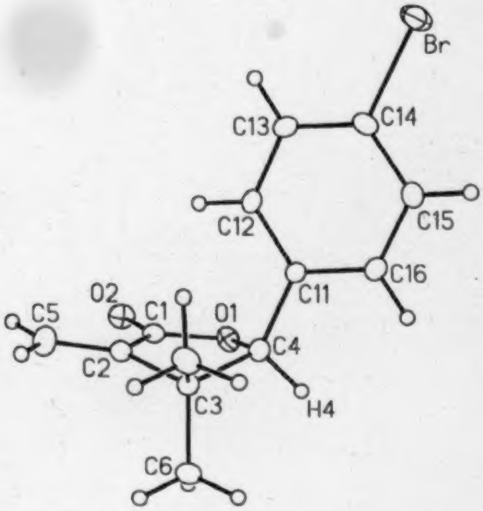


Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{13}H_{13}BrO_2$
formula weight	281.14
crystal dimensions (mm)	1.01 × 0.20 × 0.14
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	10.0541 (8)
b (Å)	11.0212 (9)
c (Å)	11.2992 (9)
V (Å^3)	1252.04 (17)
Z	4
ρ_{calcd} (g cm^{-3})	1.491
μ (mm^{-1})	3.266
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.3°) (10 s exposures)
data collection 2θ limit (deg)	52.66
total data collected	5302 ($-12 \le h \le 11$, $-13 \le k \le 6$, $-14 \le l \le 13$)
independent reflections	2549 ($R_{int} = 0.0275$)
number of observed reflections (*NO*)	2126 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	Patterson search/structure expansion (*DIRDIF–99*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.6578–0.1370
data/restraints/parameters	2549 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 145
Flack absolute structure parameter[e]	0.018 (10)
goodness-of-fit (S)[f]	0.984 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0321
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.0730
largest difference peak and hole	0.409 and –0.377 e Å^{-3}

[a] Obtained from least-squares refinement of 2462 reflections with $5.16° < 2\theta < 52.25°$.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Beurskens, P. T.; Beurskens, G.; de Gelder, R.; Garcia-Granda, S.; Israel, R.; Gould, R. O.; Smits, J. M. M. (1999). The *DIRDIF-99* program system. Crystallography Laboratory, University of Nijmegen, The Netherlands.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2)]^{-1}$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	x	y	z	U_{eq}, Å^2
Br	-0.14011(3)	0.89797(3)	-0.00346(3)	0.05769(13)*
O1	0.00538(19)	0.78646(19)	0.57615(16)	0.0398(5)*
O2	-0.12167(18)	0.8743(2)	0.71389(18)	0.0461(5)*
C1	-0.0281(3)	0.8801(3)	0.6461(2)	0.0335(6)*
C2	0.0625(3)	0.9832(3)	0.6248(2)	0.0316(6)*
C3	0.1733(3)	0.9372(3)	0.5474(2)	0.0332(6)*
C4	0.1071(2)	0.8234(2)	0.4911(3)	0.0346(6)*
C5	0.0435(3)	1.0917(3)	0.6718(3)	0.0497(8)*
C6	0.2893(3)	0.8953(4)	0.6263(2)	0.0454(7)*
C7	0.2237(3)	1.0294(3)	0.4579(2)	0.0429(8)*
C11	0.0426(2)	0.8394(3)	0.3717(2)	0.0310(6)*
C12	-0.0660(3)	0.9156(3)	0.3564(2)	0.0371(7)*
C13	-0.1231(3)	0.9317(3)	0.2454(2)	0.0391(7)*
C14	-0.0702(3)	0.8707(2)	0.1510(2)	0.0345(6)*
C15	0.0361(2)	0.7931(3)	0.1635(3)	0.0359(6)*
C16	0.0923(3)	0.7789(3)	0.2737(3)	0.0342(6)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Br	C14	1.906(3)	C3	C7	1.521(4)
O1	C1	1.343(3)	C4	C11	1.507(4)
O1	C4	1.461(3)	C11	C12	1.389(4)
O2	C1	1.214(3)	C11	C16	1.386(4)
C1	C2	1.476(4)	C12	C13	1.390(4)
C2	C3	1.504(4)	C13	C14	1.368(4)
C2	C5	1.322(4)	C14	C15	1.376(4)
C3	C4	1.556(4)	C15	C16	1.376(4)
C3	C6	1.540(4)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C4	110.4(2)	O1	C4	C3	104.8(2)
O1	C1	O2	121.7(3)	O1	C4	C11	108.7(2)
O1	C1	C2	109.9(2)	C3	C4	C11	117.1(2)
O2	C1	C2	128.4(3)	C4	C11	C12	121.4(2)
C1	C2	C3	107.0(2)	C4	C11	C16	120.3(2)
C1	C2	C5	122.8(3)	C12	C11	C16	118.3(2)
C3	C2	C5	130.2(3)	C11	C12	C13	121.0(3)
C2	C3	C4	101.1(2)	C12	C13	C14	118.7(2)
C2	C3	C6	109.0(2)	Br	C14	C13	119.6(2)
C2	C3	C7	114.1(2)	Br	C14	C15	118.6(2)
C4	C3	C6	108.6(2)	C13	C14	C15	121.8(2)
C4	C3	C7	114.2(2)	C14	C15	C16	118.9(3)
C6	C3	C7	109.4(2)	C11	C16	C15	121.3(3)

Appendix D

Structure Report for α-Methyl Lactone 39d (Chapter 3)

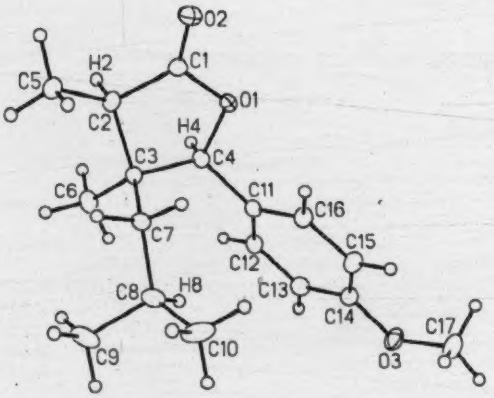
University of Alberta Department of Chemistry

X-Ray Crystallography Laboratory

XCL Code: DGH0202
Date: 5 April 2002

Compound: 5-*p*-Anisyl-4-*i*-butyl-3,4-dimethyl-2-oxotetrahydrofuran
Formula: $C_{17}H_{24}O_3$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



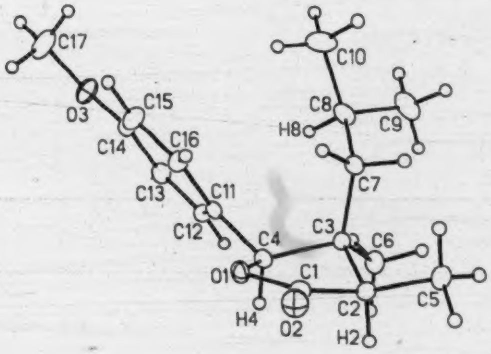


Table 1. Crystallographic Experimental Details

A. Crystal Data

formula	$C_{17}H_{24}O_3$
formula weight	276.36
crystal dimensions (mm)	0.52 × 0.24 × 0.03
crystal system	orthorhombic
space group	*Pbca* (No. 61)
unit cell parameters[a]	
a (Å)	12.3717 (11)
b (Å)	7.7720 (7)
c (Å)	32.821 (3)
V (Å^3)	3155.8 (5)
Z	8
ρ_{calcd} (g cm^{-3})	1.163
μ (mm^{-1})	0.078

B. Data Collection and Refinement Conditions

diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.2°) (25 s exposures)
data collection 2θ limit (deg)	52.80
total data collected	17050 ($-15 \le h \le 15$, $-9 \le k \le 9$, $-40 \le l \le 40$)
independent reflections	3216 ($R_{\text{int}} = 0.0973$)
number of observed reflections (*NO*)	1975 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9977–0.9605
data/restraints/parameters	3216 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 181
goodness-of-fit (*S*)[e]	1.033 [$F_o^2 \ge -3\sigma(F_o^2)$]
final *R* indices[f]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0650
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1295
largest difference peak and hole	0.191 and –0.173 e Å^{-3}

[a] Obtained from least-squares refinement of 4478 reflections with $5.96° < 2\theta < 51.63°$.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c] Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

[e]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0381P)^2 + 1.6070P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[f]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1	0.23473(12)	0.3421(2)	0.41042(5)	0.0357(4)*
O2	0.30561(14)	0.2589(2)	0.46950(6)	0.0466(5)*
O3	0.12786(15)	0.2198(2)	0.22618(5)	0.0497(5)*
C1	0.22729(19)	0.3035(3)	0.45060(8)	0.0323(6)*
C2	0.11298(18)	0.3248(3)	0.46430(7)	0.0306(6)*
C3	0.04731(18)	0.3000(3)	0.42445(7)	0.0272(5)*
C4	0.12831(18)	0.3850(3)	0.39434(7)	0.0297(6)*
C5	0.0865(2)	0.2155(3)	0.50145(8)	0.0391(6)*
C6	-0.05842(19)	0.4008(3)	0.42562(8)	0.0412(7)*
C7	0.03096(18)	0.1075(3)	0.41599(7)	0.0303(6)*
C8	-0.0451(2)	0.0508(3)	0.38116(8)	0.0395(7)*
C9	-0.1618(2)	0.0309(4)	0.39557(10)	0.0601(9)*
C10	-0.0053(3)	-0.1192(4)	0.36384(10)	0.0641(10)*
C11	0.12725(17)	0.3367(3)	0.34992(8)	0.0287(5)*
C12	0.06433(18)	0.4256(3)	0.32196(8)	0.0331(6)*
C13	0.06475(19)	0.3820(3)	0.28113(8)	0.0374(6)*
C14	0.12955(19)	0.2495(3)	0.26744(8)	0.0355(6)*
C15	0.1927(2)	0.1605(3)	0.29460(8)	0.0407(7)*
C16	0.19070(19)	0.2040(3)	0.33554(8)	0.0360(6)*
C17	0.2029(2)	0.0987(4)	0.21071(9)	0.0640(9)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C1	1.356(3)	C4	C11	1.505(3)
O1	C4	1.457(3)	C7	C8	1.545(3)
O2	C1	1.202(3)	C8	C9	1.528(4)
O3	C14	1.374(3)	C8	C10	1.520(4)
O3	C17	1.416(3)	C11	C12	1.388(3)
C1	C2	1.493(3)	C11	C16	1.380(3)
C2	C3	1.552(3)	C12	C13	1.382(3)
C2	C5	1.521(3)	C13	C14	1.380(3)
C3	C4	1.555(3)	C14	C15	1.372(3)
C3	C6	1.525(3)	C15	C16	1.386(3)
C3	C7	1.535(3)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O1	C4	109.98(17)	C3	C4	C11	120.25(19)
C14	O3	C17	117.1(2)	C3	C7	C8	119.49(19)
O1	C1	O2	120.7(2)	C7	C8	C9	112.1(2)
O1	C1	C2	109.4(2)	C7	C8	C10	109.1(2)
O2	C1	C2	129.8(2)	C9	C8	C10	109.5(2)
C1	C2	C3	103.20(19)	C4	C11	C12	121.4(2)
C1	C2	C5	112.5(2)	C4	C11	C16	120.9(2)
C3	C2	C5	119.58(19)	C12	C11	C16	117.7(2)
C2	C3	C4	98.37(17)	C11	C12	C13	121.1(2)
C2	C3	C6	111.3(2)	C12	C13	C14	120.0(2)
C2	C3	C7	110.02(18)	O3	C14	C13	115.9(2)
C4	C3	C6	110.51(19)	O3	C14	C15	124.4(2)
C4	C3	C7	112.60(19)	C13	C14	C15	119.7(2)
C6	C3	C7	113.09(19)	C14	C15	C16	119.8(2)
O1	C4	C3	104.77(17)	C11	C16	C15	121.6(2)
O1	C4	C11	107.55(18)				

Appendix E

Structure Report for Acrylanilide 13b (Chapter 5)

University of Alberta Department of Chemistry

X-Ray Crystallography Laboratory

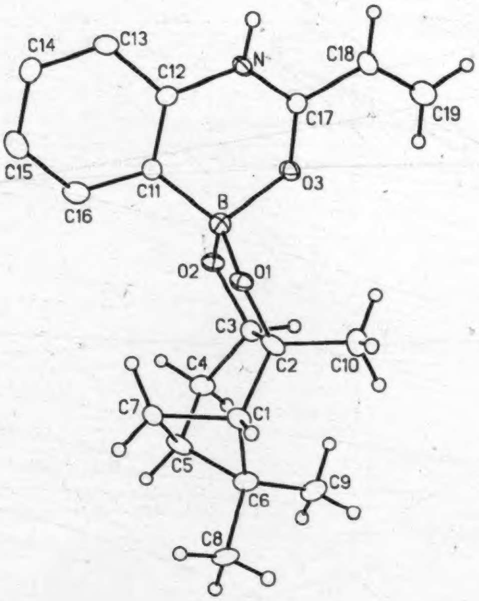
XCL Code: DGH9911

Date: 13 December 1999

Compound: (1*S*,2*S*,3*R*,5*S*)-Pinanediol ({2-acrylamido}phenyl)boronate, di(chloroform) solvate

Formula: $C_{21}H_{26}BCl_6NO_3$ ($C_{19}H_{24}BNO_3{\bullet}2CHCl_3$)

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



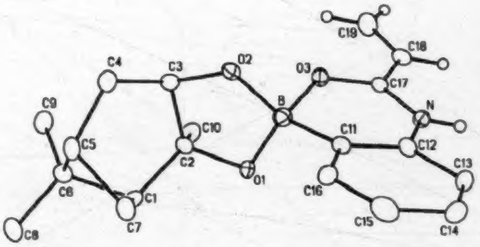


Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{21}H_{26}BCl_6NO_3$
formula weight	563.94
crystal dimensions (mm)	0.38 × 0.06 × 0.04
crystal system	monoclinic
space group	$P2_1$ (No. 4)
unit cell parameters[a]	
a (Å)	11.170 (5)
b (Å)	10.121 (6)
c (Å)	11.545 (7)
β (deg)	94.627 (11)
V (Å^3)	1301.0 (12)
Z	2
ρ_{calcd} (g cm^{-3})	1.440
μ (mm^{-1})	0.684
B. Data Collection and Refinement Conditions	
diffractometer	Bruker P4/RA/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ϕ rotations (0.3°) / ω scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	53.90
total data collected	6476 ($-5 \leq h \leq 14$, $-12 \leq k \leq 12$, $-14 \leq l \leq 14$)
independent reflections	5222 ($R_{\text{int}} = 0.0672$)
number of observations (*NO*)	2120 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9737–0.8385
data/restraints/parameters	5222 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 284
Flack absolute structure parameter[e]	0.15 (14)
goodness-of-fit (S)[f]	0.858 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0713
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.2217
largest difference peak and hole	0.335 and –0.403 e Å^{-3}

[a] Obtained from least-squares refinement of 1857 centered reflections.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.1015P)^2]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

(a) atoms of (1S,2S,3R,5S)-pinanediol ({2-acrylamido}phenyl)boronate

Atom	x	y	z	U_{eq}, Å^2
O1	0.3134(5)	0.2895(5)	-0.2327(4)	0.0316(14)*
O2	0.3794(4)	0.0849(5)	-0.1691(5)	0.0337(14)*
O3	0.3699(5)	0.2561(6)	-0.0241(5)	0.0356(14)*
N	0.5209(6)	0.4056(7)	0.0127(6)	0.0299(17)*
C1	0.1808(8)	0.2071(8)	-0.3909(7)	0.033(2)*
C2	0.2132(8)	0.2017(8)	-0.2604(7)	0.035(2)*
C3	0.2572(7)	0.0621(8)	-0.2216(7)	0.034(2)*
C4	0.2644(8)	-0.0422(9)	-0.3171(8)	0.043(2)*
C5	0.2291(8)	0.0110(9)	-0.4351(8)	0.044(2)*
C6	0.1068(7)	0.0878(9)	-0.4395(7)	0.039(2)*
C7	0.2909(8)	0.1467(9)	-0.4508(8)	0.040(2)*
C8	0.0553(7)	0.1103(12)	-0.5645(8)	0.050(3)*
C9	0.0066(8)	0.0261(10)	-0.3725(8)	0.048(3)*
C10	0.1116(7)	0.2510(9)	-0.1928(8)	0.043(2)*
C11	0.5366(7)	0.2787(8)	-0.1642(7)	0.0300(19)*
C12	0.5836(7)	0.3698(9)	-0.0847(7)	0.031(2)*
C13	0.6948(7)	0.4300(9)	-0.0977(7)	0.035(2)*
C14	0.7603(8)	0.3959(9)	-0.1870(8)	0.041(2)*
C15	0.7163(9)	0.3012(10)	-0.2658(8)	0.050(3)*
C16	0.6064(8)	0.2441(9)	-0.2553(8)	0.043(2)*
C17	0.4248(7)	0.3440(8)	0.0410(7)	0.028(2)*
C18	0.3767(8)	0.3801(8)	0.1502(7)	0.033(2)*
C19	0.2806(9)	0.3249(11)	0.1906(9)	0.056(3)*
B	0.4022(9)	0.2247(10)	-0.1544(9)	0.035(2)

(b) solvent chloroform atoms

Atom	x	y	z	U_{eq}, Å^2
Cl1S	-0.4975(2)	0.1133(3)	0.3148(2)	0.0558(7)*
Cl2S	-0.4640(3)	-0.0675(3)	0.5079(2)	0.0688(9)*
Cl3S	-0.2694(2)	0.0978(4)	0.4462(3)	0.0850(10)*
C1S	-0.3973(8)	0.0110(10)	0.3946(8)	0.048(3)*
Cl4S	-0.2717(2)	0.1105(4)	0.1032(3)	0.0816(10)*
Cl5S	-0.0653(3)	0.0206(3)	-0.0134(3)	0.0806(10)*
Cl6S	-0.0479(3)	0.2475(4)	0.1337(3)	0.1058(13)*
C2S	-0.1442(9)	0.1570(10)	0.0352(9)	0.060(3)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

(a) within (1S,2S,3R,5S)-pinanediol ({2-acrylamido}phenyl)boronate

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O1	C2	1.445(10)	C4	C5	1.488(12)
O1	B	1.444(11)	C5	C6	1.569(13)
O2	C3	1.467(9)	C5	C7	1.554(13)
O2	B	1.445(12)	C6	C8	1.526(12)
O3	C17	1.287(9)	C6	C9	1.543(12)
O3	B	1.607(12)	C11	C12	1.375(11)
N	C12	1.418(11)	C11	C16	1.403(12)
N	C17	1.307(10)	C11	B	1.611(13)
C1	C2	1.521(11)	C12	C13	1.402(12)
C1	C6	1.543(12)	C13	C14	1.356(12)
C1	C7	1.582(12)	C14	C15	1.384(13)
C2	C3	1.550(12)	C15	C16	1.371(12)
C2	C10	1.513(12)	C17	C18	1.456(12)
C3	C4	1.533(12)	C18	C19	1.329(13)

(b) within the solvent chloroform molecules

Atom1	Atom2	Distance	Atom1	Atom2	Distance
Cl1S	C1S	1.734(10)	Cl4S	C2S	1.745(11)
Cl2S	C1S	1.748(10)	Cl5S	C2S	1.755(11)
Cl3S	C1S	1.742(9)	Cl6S	C2S	1.759(11)

Table 4. Selected Interatomic Angles (deg)

(a) within (1S,2S,3R,5S)-pinanediol ({2-acrylamido}phenyl)boronate

Atom1	Atom2	Atom3	Angle
C2	O1	B	109.8(6)
C3	O2	B	110.6(6)
C17	O3	B	123.4(6)
C12	N	C17	123.0(7)
C2	C1	C6	114.2(7)
C2	C1	C7	106.7(7)
C6	C1	C7	87.2(6)
O1	C2	C1	108.4(7)
O1	C2	C3	106.0(6)
O1	C2	C10	106.5(7)
C1	C2	C3	111.3(7)
C1	C2	C10	111.7(7)
C3	C2	C10	112.6(8)
O2	C3	C2	103.8(6)
O2	C3	C4	107.7(7)
C2	C3	C4	117.0(7)
C3	C4	C5	112.6(7)
C4	C5	C6	112.1(8)
C4	C5	C7	109.8(7)
C6	C5	C7	87.3(7)
C1	C6	C5	86.3(6)
C1	C6	C8	112.2(8)
C1	C6	C9	121.6(7)
C5	C6	C8	111.4(7)
C5	C6	C9	116.6(7)
C8	C6	C9	107.5(6)
C1	C7	C5	85.5(6)
C12	C11	C16	117.6(8)
C12	C11	B	119.2(7)
C16	C11	B	123.0(8)
N	C12	C11	120.9(7)
N	C12	C13	118.2(8)
C11	C12	C13	120.9(8)
C12	C13	C14	120.5(8)
C13	C14	C15	119.4(8)
C14	C15	C16	120.5(9)
C11	C16	C15	121.1(9)
O3	C17	N	123.1(8)
O3	C17	C18	119.2(8)
N	C17	C18	117.7(8)
C17	C18	C19	124.3(9)
O1	B	O2	105.4(7)
O1	B	O3	107.6(7)
O1	B	C11	113.5(7)
O2	B	O3	104.6(7)
O2	B	C11	118.7(8)
O3	B	C11	106.2(7)

(b) within the solvent chloroform molecules

Atom1	Atom2	Atom3	Angle
Cl1S	C1S	Cl2S	111.9(5)
Cl1S	C1S	Cl3S	110.9(6)
Cl2S	C1S	Cl3S	111.1(5)
Cl4S	C2S	Cl5S	112.4(6)
Cl4S	C2S	Cl6S	109.1(6)
Cl5S	C2S	Cl6S	108.7(6)